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NOTICE

The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

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ALTERNATE REPRESENTATIVE

RICHARD P. STRONG, M.D.

ASSOCIATION OF AMERICAN PHYSICIANS

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REPRESENTATIVE ON THE EXECUTIVE COMMITTEE OF THE CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS

THEODORE C. JANEWAY, M.D.

ALTERNATE REPRESENTATIVE

RICHARD P. STRONG, M.D.

OFFICERS OF THE ASSOCIATION

FROM ITS ORGANIZATION TO THE PRESENT TIME

Year	*President.*	*Vice-President.*	*Recorder.*	*Secretary.*	*Treasurer.*
1886.	Francis A. Delafield	.....	.....	James Tyson.	A. B. Ball.
1887.	S. Weir Mitchell.	Francis Minot. R. Palmer Howard.	J. T. Whittaker.	G. L. Peabody.	W. W. Johnston.
1888.	Wm. H. Draper.	Francis Minot. R. Palmer Howard	William Osler.	Henry Hun.	W. W. Johnston.
1889.	Francis Minot.	R. Palmer Howard. S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1900.	E. G. Janeway.	Wm. H. Welch.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1901.	Wm. H. Welch.	H. P. Walcott.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1902.	James C. Wilson.	Jas. Stewart.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1903.	James Stewart.	W. T. Councilman.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1904.	W. T. Councilman.	E. L. Trudeau.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1905.	E. L. Trudeau.	Frank Billings.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1906.	Frank Billings.	F. P. Kinnicutt.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1907.	F. P. Kinnicutt.	James Tyson.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1908.	James Tyson.	V. C. Vaughan.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1909.	V. C. Vaughan.	Henry Hun.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1910.	Henry Hun.	F. Forchheimer.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1911.	F. Forchheimer.	J. George Adami.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1912.	J. George Adami.	L. F. Barker.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1913.	L. F. Barker.	Simon Flexner.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1914.	Simon Flexner.	S. J. Meltzer.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1915.	S. J. Meltzer.	Henry Sewall.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1916.	Henry Sewall.	George Dock.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1917.	George Dock.	F. H. Williams.	T. R. Boggs.	T. McCrae.	J. P. C. Griffith.

ACTIVE MEMBERS

ELECTED

1892. Abbott, Alexander C., Laboratory of Hygiene, University of Pennsylvania, Philadelphia.
1896. Abel, John J., Johns Hopkins Medical School, Baltimore, Md.
1894. Adami, J. George, Pathological Laboratory, McGill University, Montreal, Canada.
1905. Adams, Samuel S., 1801 Connecticut Ave., Washington, D. C.
1896. Adler, Isaac, 401 West End Ave., New York.
1911. Anders, James M., 1605 Walnut St., Philadelphia.
1913. Anderson, John F., E. R. Squibb's Lab., New Brunswick, N. J.
1911. Ashford, Bailey K., U. S. Army, San Juan, P. R.
1913. Auer, John, Rockefeller Institute, 66th St. and Ave. A, New York.
1905. Babcock, Robert H., 77 East Washington St., Chicago.
1908. Baldwin, E. R., Saranac Lake, N. Y.
1899. Barker, L. F., 1035 North Calvert St., Baltimore, Maryland.
1916. Bass, Charles C., Tulane Univ., New Orleans.
1894. Biggs, Herman M., 5 West 58th St., New York.
1895. Billings, Frank, 122 S. Michigan Blvd., Chicago.
1901. Blumer, George, 204 York St., New Haven, Conn.
1913. Boggs, Thomas R., 21 West Chase St., Baltimore, Md.
1890. Bond, Charles S., 112 North 10th St., Richmond, Ind.
1898. Brannan, John W., 48 W. 51st St., New York.
1915. Brill, Nathan E., 48 W. 76th St., New York.
1913. Brooks, Harlow, 44 West 9th St., New York.
1911. Brown, Lawrason, 104 Main St., Saranac Lake, N. Y.
1914. Brown, Thomas R., 19 W. Biddle St., Baltimore.
1904. Brown, Philip K., 516 Sutter St., San Francisco, Cal.
1913. Bunting, C. H., University of Wisconsin, Madison.
1899. Cabot, R. C., 1 Marlborough St., Boston.
1912. Camac, C. N. B., 128 E. 60th St., New York.
1914. Cannon, Walter B., Harvard Medical School, Boston.
1908. Capps, Joseph A., 150 Michigan Ave., Chicago.
1907. Christian, Henry A., 252 Marlboro St., Boston.
1898. Cohen, Solomon Solis, 1525 Walnut St., Philadelphia.

ELECTED

1909. Cole, Rufus I., 960 Park Ave., New York.
1914. Coleman, Warren, 58 West 55th St., New York.
1904. Collins, Joseph, 37 West 54th St., New York.
1908. Conner, Lewis A., 121 East 62d St., New York.
1906. Coplin, W. M. L., 606 South 48th St., Philadelphia.
1893. Dock, George, 600 S. Kingshighway, St. Louis, Missouri.
1904. Edsall, David L., 80 Marlborough St., Boston, Mass.
1901. Edwards, Arthur R., 100 State St., Chicago.
1915. Emerson, Charles P., Medical School, University of Indiana, Indianapolis.
1915. Erlanger, Joseph, 600 S. Kingshighway, St. Louis.
1888. Ernst, Harold C., 8 Greenough Ave., Jamaica Plain, Mass.
1900. Ewing, James, 260 West 57th St., New York.
1904. Finley, Frederick G., 1013 Dorchester St., Montreal, Canada.
1895. Flexner, Simon, Rockefeller Institute for Medical Research, 66th Street and Avenue A, New York.
1913. Ford, W. W., 1134 Cathedral St., Baltimore, Md.
1916. Foster, Nellis B., University Hospital, Ann Arbor, Mich.
1908. Freeman, R. G., 211 W. 57th St., New York.
1913. Friedenwald, Julius, 1013 N. Charles St., Baltimore, Md.
1894. Fussell, M. Howard, 421 Lyceum Ave., Manayunk, Phila.
1903. Futcher, Thomas B., 23 West Franklin St., Baltimore.
1914. Gay, Frederick P., University of California, Berkeley.
1904. Gordinier, H. C., 89 4th St., Troy, N. Y.
1901. Greene, Charles L., 150 Lowry Arcade, St. Paul.
1890. Griffith, J. P. Crozer, 1810 Spruce St., Philadelphia.
1908. Hamilton, W. F., 287 Mountain St., Montreal, Canada.
1915. Hamman, Louis V., 714 Park Ave., Baltimore.
1890. Hare, Hobart A., 1801 Spruce St., Philadelphia.
1898. Herrick, James B., People's Gas Building, Chicago.
1910. Hewlett, Albion W., Stanford Med. School, San Francisco, Cal.
1900. Holt, L. E., 14 West 55th St., New York.
1911. Hoover, C. F., 702 Rose Building, Cleveland, Ohio.
1914. Howard, Campbell P., Iowa City, Iowa.
1911. Howard, W. T., 1213 N. Calvert St., Baltimore.
1911. Howland, John, Johns Hopkins Hospital, Baltimore, Md.
1916. Hunt, J. Ramsay, 20 W. 50th St., New York.
1907. Hunt, Reid, Harvard Med. School, Boston.
1901. Jackson, Henry, 380 Marlborough St., Boston.
1908. Janeway, Theodore C., Johns Hopkins Hospital, Baltimore.
1916. Jobling, James W., Vanderbilt Univ., Nashville, Tenn.
1902. Joslin, E. P., 81 Bay State Road, Boston.
1916. Karsner, Howard T., Lakeside Hospital, Cleveland.

ELECTED

1901. Kinyoun, J. J., 1421 Clifton St., Washington, D. C.
1915. Klotz, Oskar, University of Pittsburgh, Pittsburgh.
1900. Koplik, Henry, 30 East 62d St., New York.
1895. Lafleur, Henri A., 251 Peel St., Montreal, Canada.
1906. Lambert, Samuel W., 130 East 35th St., New York.
1915. Landis, H. R. M., 11 S. 21st St., Philadelphia.
1888. Lewis, Morris J., 1316 Locust St., Philadelphia.
1910. Libman, E., 180 East 64th St., New York.
1912. Locke, Edwin A., 311 Beacon St., Boston.
1911. Loeb, Leo, 600 S. Kingshighway, St. Louis.
1909. Longcope, Warfield T., 41 E. 70th St., New York.
1910. Lord, Frederick T., 305 Beacon St., Boston.
1914. McCrae, John, 160 Metcalf Street, Montreal.
1905. McCrae, Thomas, 1627 Spruce St., Philadelphia.
1891. McPhedran, A., 151 Bloor St., Toronto, Canada.
1902. MacCallum, W. G., 981 Madison Ave., New York.
1905. Macallum, A. B., University of Toronto, Toronto, Canada.
1903. Martin, Charles F., 33 Durocher St., Montreal, Canada.
1892. Meltzer, S. J., 13 West 121st St., New York.
1905. Meyer, Adolph, Johns Hopkins Medical School, Baltimore.
1905. Miller, Joseph L., 122 S. Michigan Boulevard, Chicago.
1898. Mitchell, John K., 1730 Spruce St., Philadelphia.
1908. Moffitt, Herbert C., 240 Stockton St., San Francisco, Cal.
1915. Morris, Roger S., Cincinnati General Hospital, Cincinnati.
1915. Noguchi, Hideyo, Rockefeller Institute, 66th St. and Ave. A, New York.
1914. Norris, Geo. W., 1530 Locust Street, Philadelphia.
1891. Northrup, W. P., 57 East 79th St., New York.
1900. Novy, F. G., University of Michigan, Ann Arbor, Michigan.
1902. Opie, E. L., 600 S. Kingshighway, St. Louis, Missouri.
1899. Park, Wm. H., 315 West 76th St., New York.
1916. Peabody, Francis W., Peter Bent Brigham Hospital, Boston.
1904. Pearce, R. M., Medical School, Univ. of Penna., Philadelphia.
1909. Pratt, Joseph H., 317 Marlborough St., Boston.
1903. Preble, Robert B., 590 Dearborn Ave., Chicago.
1899. Prince, Morton, 458 Beacon St., Boston.
1894. Rachford, B. K., 1961 Madison Rd., Cincinnati.
1904. Richardson, Mark W., 67 Milk St., Boston.
1905. Riesman, David, 1715 Spruce St., Philadelphia.
1915. Robinson, G. Canby, 600 S. Kingshighway, St. Louis.
1907. Rosenau, M. J., Harvard Medical School, Boston, Mass.
1916. Rous, Peyton, 131 E. 19th St., New York.
1915. Rowntree, Leonard G., Univ. of Minn., Minneapolis.

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1911. Rudolf, Robert D., 396 Bloor St., Toronto, Canada.
1911. Russell, Frederick F., Surgeon-General's Office, U. S. Army, Washington, D. C.
1898. Sachs, B., 116 W. 59th St., New York.
1908. Sailer, Joseph, 1718 Spruce St., Philadelphia.
1900. Sewall, Henry, 1360 Vine St., Denver, Col.
1902. Sippy, B. W., 122 S. Michigan Avenue, Chicago, Ill.
1892. Smith, Theobald B., Princeton, N. J.
1907. Sollmann, Torald H., 4327 Superior Ave., Cleveland.
1915. Southard, Elmer E., 74 Fenwood Road, Boston.
1916. Steiner, Walter R., 4 Trinity St., Hartford, Conn.
1898. Stengel, Alfred, 1728 Spruce St., Philadelphia.
1889. Stockton, Charles G., 436 Franklin St., Buffalo, N. Y.
1911. Strong, R. P., Harvard Medical School, Boston.
1916. Taussig, Albert E., Metropolitan Bldg., St. Louis.
1907. Taylor, A. E., University of Pennsylvania, Philadelphia.
1899. Thacher, J. S., 20 West 50th St., New York.
1897. Thayer, W. S., 406 Cathedral St., Baltimore.
1889. Thompson, W. Gilman, 61 W. 49th St., New York.
1889. Thomson, Wm. H., 71 Central Park, West, New York.
1912. Tileston, Wilder, 424 Temple St., New Haven.
1898. Vickery, Herman F., 263 Beacon St., Boston.
1914. Wadsworth, Aug. B., 278 Yates St., Albany.
1901. Warthin, Aldred S., Univ. of Michigan, Ann Arbor, Mich.
1906. Weaver, George H., 1743 W. Harrison St., Chicago.
1912. Wells, H. G., Sprague Memorial Institute, Chicago.
1913. Whipple, Geo. H., Hooper Foundation, University of California Hospital, San Francisco, California.
1915. White, Wm. Charles, 2851 Bedford Ave., Pittsburgh.
1894. Williams, Francis H., 505 Beacon St., Boston.
1901. Williams, Herbert U., University of Buffalo, Buffalo, N. Y.
1912. Wilson, Louis B., 1101 W. Zumbro St., Rochester, Minn.
1898. Withington, Charles F., 35 Bay State Road, Boston.
1914. Wood, Francis C., 437 W. 59th St., New York.
1916. Woodyatt, Rollin T., 104 S. Michigan Ave., Chicago.

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1916. Allen, Frederick M., Rockefeller Institute, 66th St. and Ave. A, New York.
1915. Cohn, Alfred E , 315 Central Park West, New York.
1916. Dochez, Alphonse R., Rockefeller Institute, 66th St. and Ave. A, New York.
1913. Duval, Charles W., Tulane University, New Orleans.
1916. Edmunds, Charles W., Univ. of Michigan, Ann Arbor, Mich.
1915. Einhorn, Max, 20 E. 63d St., New York.
1916. Eyster, John H., Univ. of Wisconsin, Madison, Wis.
1915. Frothingham, Jr., Channing, 395 Marlborough St., Boston.
1916. Hirschfelder, Arthur D., Univ. of Minnesota, Minneapolis.
1915. Irons, Ernest E., 122 S. Michigan Ave., Chicago.
1915. Lee, Roger I., Harvard Med. School, Boston.
1916. Loevenhart, Arthur S., Univ. of Wisconsin, Madison, Wis.
1915. Miller, James Alex., 379 Park Ave., New York.
1916. Mosenthal, Herman O., The Johns Hopkins Hospital, Baltimore.
1914. Ordway, Thomas, Albany Med. School, Albany, N. Y.
1914. Pemberton, Ralph, 2224 Locust St., Philadelphia.
1914. Plummer, H. S., Rochester, Minn.
1916. Rosenow, Edward C., Mayo Clinic, Rochester, Minn.
1916. Shattuck, George C., 135 Marlborough St., Boston.
1914. Smith, Elsworth, Humboldt Building, St. Louis.
1915. Swift, Homer F., 65 Central Park, West, New York.
1916. Webb, Gerald B., Burns Bldg., Colorado Springs, Col.
1913. White, Franklin W., 322 Marlborough St., Boston.
1915. Wolbach, S. Burt, 420 Beacon St., Boston.
1914. Wood, Edward Jenner, 201 Chestnut St., Wilmington, N. C.

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* Original Members.

ELECTED ACTIVE MEMBER	ELECTED HONORARY MEMBER	
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*1886.	1915.	HUN, HENRY, 149 Washington Ave., Albany.
*1886.	1912.	JACOBI, A., 19 East 47th St., New York.
1902.	1916.	KOBER, GEO. M., 1819 Q St., N. W., Washington.
*1886.	1912.	OSLER, WM., Oxford University, England.
*1886.	1913.	PRUDDEN, T. MITCHELL, 160 W. 59th St., New York.
*1886.	1915.	TYSON, JAMES, 1506 Spruce St., Philadelphia.
1889.	1915.	VAUGHAN, VICTOR C., Univ. of Michigan, Ann Arbor.
*1886.	1913.	WELCH, WILLIAM H., 807 St. Paul St., Baltimore.

EMERITUS MEMBERS

* Original Members

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
1898.	1916.	Blackader, A. D., 236 Mountain St., Montreal.
1892.	1916.	Bolton, Meade B., Charlottesville, Va.
1888.	1910.	Bridge, Norman, 10 Chester Place, Los Angeles, Cal.
1889.	1916.	Cary, Charles, 340 Delaware Ave., Buffalo.
*1886.	1906.	Councilman, Wm. T., 78 Bay State Road, Boston.
1897.	1905.	Cushny, Arthur C., University of London, London, England.
1894.	1908.	Cutler, Elbridge G., 214 Beacon St., Boston.
1888.	1916.	Dana, Charles L., 53 W. 53d St., New York.
*1886.	1905.	Edes, Robert T., 340 Summer Ave., Reading, Mass.
1890.	1902.	Fisk, S. A. Brimfield, Mass.
*1886.	1900.	Guitéras, John, Havana, Cuba.
*1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1897.	1910.	Hektoen, Ludvig, 637 S. Wood St., Chicago.
*1886.	1908.	Henry, Frederick P., 114 S. 18th St., Philadelphia
1890.	1902.	Hurd, H. M. Johns Hopkins Hospital, Baltimore.
1899.	1914.	James, Walter B., 17 W. 54th St., New York.
1898.	1916.	Mallory, F. B., Harvard Medical School, Boston.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
1901.	1913.	Morse, John L., 70 Bay State Road, Boston.
1898.	1914.	Pfaff, Franz, Dresdner Bank, Berlin.
*1886.	1898.	Polk, Wm. M., 7 East 36th St., New York.
*1886.	1915.	Putnam, James J., 106 Marlborough St., Boston.
*1886.	1904.	Robinson, Beverley, 42 West 37th St., New York.
1900.	1914.	Sears, Geo. G., 19 Marlborough St., Boston, Mass.
*1886.	1912.	Shattuck, Frederick C., 135 Marlborough Street, Boston.
*1886.	1905.	Shattuck, George B., 183 Beacon St., Boston.
1887.	1902.	Starr, Louis, 1818 S. Rittenhouse Square, Phila.
1887.	1911.	Starr, M. Allen, 5 West 54th St., New York.
1889.	1904.	Walcott, Henry P., 11 Waterhouse St., Cabridgem, Mass.

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
1898.	1915.	Wesbrook, F. F., Univ. British Columbia, Vancouver, B. C.
*1886.	1911.	Wilkins, George, 899 Dorchester St., Montreal.
*1886.	1911.	Wilson, James C., 1509 Walnut St., Philadelphia.
*1886.	1908.	Wood, Horatio C, 4107 Chester Ave., Philadelphia.
1899.	1912.	Wright, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

DECEASED MEMBERS

* Original Members

DATE OF ELECTION

*1886. Atkinson, I. E., Baltimore.
*1886. Ball, A. Brayton, New York.
1890. Barker, Fordyce, New York.
*1886. Baumgarten, G., St. Louis.
*1886. Billings, John S., New York.
*1886. Bowditch, Henry I., Boston.
*1886. Bruen, Edward T., Philadelphia.
*1886. Busey, Samuel C., Washington, D. C.
1907. Carroll, James, Washington, D. C.
*1886. Chew, Samuel C., Baltimore.
*1886. Clark, Alonzo, New York.
*1886. Clymer, Meredith, New York.
*1886. Da Costa, J. M., Philadelphia.
1889. Dabney, William C., University of Virginia.
*1886. Dalton, John C., New York.
*1886. Dana, Israel T., Portland, Maine.
1888. Danforth, I. N., Chicago.
*1886. Delafield, Francis A., New York.
*1886. Donaldson, Frank, Baltimore.
*1886. Draper, William H., New York.
1899. Ely, John Slade, New Haven, Conn.
1895. Fischel, William E., St. Louis.
*1886. Fitz, Reginald H., Boston.
*1886. Folsom, Chas. F., Boston.
*1886. Forchheimer, F., Cincinnati.
*1886. Formad, Henry F., Philadelphia.
1889. Geddings, W. H., Atken, S. C.
*1886. Graham, J. E., Toronto, Canada.
1898. Herter, C. A., New York.
*1886. Howard, R. Palmer, Montreal, Canada.
*1886. Hudson, Jr., E. Darwin, New York.
*1886. Hutchinson, James H., Philadelphia.
*1886. Janeway, E. G., New York.

DATE OF ELECTION

*1886. Johnson, Hosmer A., Chicago.
1899. Johnston, W. G., Montreal, Canada.
*1886. Johnston, W. W., Washington, D. C.
1902. Kelly, A. O. J., Philadelphia.
*1886. Kinnicutt, Francis P., New York.
1890. Latimer, Thomas S., Baltimore.
*1886. Leidy, Joseph, Philadelphia.
*1886. Longstreth, Morris, Cambridge, Mass.
*1886. Loomis, Alfred L., New York.
1889. Loving, Starling, Columbus, O.
*1886. Lyman, Henry M., Chicago.
1890. MacDonnell, R. P., Montreal, Canada.
*1886. McBride, Thomas A., New York.
1887. Meigs, Arthur V., Philadelphia.
*1886. Metcalfe, John T., Cold Springs, N. Y.
*1886. Miles, F. T., Baltimore.
*1886. Minot, Francis, Boston.
*1886. Mitchell, S. Weir, Philadelphia.
1887. Musser, John H., Philadelphia.
1898. Packard, Frederick A., Philadelphia.
*1886. Peabody, George L., Newport, R. I.
*1886. Pepper, William, Philadelphia.
1888. Prentiss, D. W., Washington, D. C.
1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo, N. Y.
1889. Roosevelt, J. West, New York.
*1886. Ross, George, Montreal, Canada.
1893. Rotch, Thomas M., Boston.
*1886. Schmidt, H. D., New Orleans.
*1886. Sinkler, Wharton, Philadelphia.
*1886. Smith, A. A., New York.
1891. Smith, Andrew H., New York.
1905. Steele, J. Dutton, Philadelphia.
*1886. Sternberg, Geo. M., Washington.
1896. Stewart, D. D., Philadelphia.
*1886. Stewart, James, Montreal, Canada.
*1886. Stillé, Alfred, Philadelphia.
*1886. Thacher, James K., New Haven, Conn.
*1886. Trudeau, Edward L., Saranac Lake.
*1886. Ward, Samuel B., Albany.
*1886. Whittaker, James T., Cincinnati.

ASSOCIATION

OF

AMERICAN PHYSICIANS

CONSTITUTION

As Amended May 10, 1916

ARTICLE I

OBJECT AND NAME

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

ARTICLE II

MEMBERS

The number of active members shall be limited to one hundred and sixty. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to emeritus membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of honorary members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Provided, That in case of removal of an active member to a locality so distant that his attendance at the annual meetings may reasonably be regarded as impossible, the Council may be empowered, should it so desire, to transfer the name of such a member during his absence to the list of emeritus members, without regard to the length of his previous active membership.

ARTICLE III

OFFICERS

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

ARTICLE IV

DUTY OF OFFICERS

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of TRANSACTIONS.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

ARTICLE V

COUNCIL

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the

Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate, and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

ARTICLE VI

MEETINGS

1. The Association shall hold an annual meeting either in the City of Washington, D. C., or at Atlantic City at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. The President shall have complete charge of, and responsibility for, the program. He shall have power to accept or reject any paper offered. He shall have power to limit the number of papers, and to assign a time limit for each one. Papers shall be presented to the Association only in abstract, and preferably shall not be read from manuscript. They may be published in full in the TRANSACTIONS as also in any other medical publication.

5. The referee, co-referee, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

ARTICLE VII

QUORUM

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum, and for altering the Constitution twenty-five members shall be necessary.

ARTICLE VIII

ELECTION OF MEMBERS

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting of the Association; and within six months of the time of nomination the

nominators shall transmit to the Council letters stating the qualifications of the nominee and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The elections of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

ARTICLE IX

ANNUAL DUES

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

ARTICLE X

AMENDMENTS TO THE CONSTITUTION

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

THIRTY-FIRST ANNUAL MEETING

Held at Washington, D. C., May 9, 10, *and* 11, 1916

The following members were present at the meeting:

Adams, Samuel S.
Adler, Isaac
Anders, Jas. M.
Anderson, Jno. F.
Ashford, Bailey K.
Auer, John
Babcock, Robt. H.
Baldwin, E. R.
Barker, L. F.
Bass, C. C.
Biggs, Herman M.
Billings, Frank
Blackader, A. D.
Blumer, George
Boggs, Thos. R.
Bond, Chas. S.
Brannan, John W.
Brill, Nathan E.
Brooks, Harlow,
Brown, Lawrason
Brown, Thos. R.
Brown, Philip K.
Bunting, C. H.
Cabot, R. C.
Cannon, W. B.
Capps, Jos. A.
Cary, Charles
Christian, Henry A.
Cohen, S. Solis
Cohn, Alfred E.
Cole, Rufus I.
Coleman, Warren
Collins, Joseph
Coplin, W. M. L.
Dana, Chas. L.
Dock, George
Duval, Chas. W.
Edsall, David L.
Edwards, Arthur R.
Einhorn, Max
Erlanger, Jos.
Ernst, Harold C.
Ewing, James
Ford, W. W.
Foster, Nellis B.
Freeman, R. G.
Friedenwald, J.
Frothingham, C., Jr.
Fussell, M. H.
Futcher, Thos. B.
Gay, Fredk. P.
Gordinier, H. C.
Griffith, J. P. C.
Hamilton, W. F.
Hamman, Louis V.
Hare, Hobart A.
Hektoen, Ludvig
Herrick, Jas. B.
Hewlett, A. W.
Holt, L. E.
Hoover, C. F.
Howard, C. P.
Howard, W. T.
Howland, John
Hunt, Reid
Irons, E. E.
Jacobi, A.
Jackson, Henry
Janeway, T. C.
Jobling, Jas. W.
Joslin, E. P.
Klotz, Oskar
Kober, Geo. M.
Koplik, Henry
Lambert, S. W.
Landis, H. R. M.
Lee, Roger I.
Lewis, M. J.
Loeb, Leo
Longcope, W. T.
Lord, F. T.
McCrae, Thos.
McPhedran, A.
Mallory, F. B.
Martin, C. F.
Meltzer, S. J.
Meyer, Adolph

Miller, Jas. A.
Miller, Jos. L.
Mitchell, Jno. K.
Morris, R. S.
Noguchi, Hideyo
Norris, Geo. W.
Novy, F. G.
Opie, E. L.
Ordway, Thos.
Park, Wm. H.
Peabody, F. W.
Pearce, R. M.
Pemberton, R.
Plummer, H. S.
Pratt, Jos. H.
Putnam, J. J.
Rachford, B. K.
Riesman, David
Rosenau, M. J.
Rous, Peyton
Rowntree, L. G.
Sachs, B.
Sailer, Jos.
Sewall, Henry
Shattuck, F. C.
Sippy, B. W.
Smith, Elsworth
Southard, E. E.
Stengel, Alfred
Stockton, C. G.
Strong, R. P.
Swift, Homer F.
Taussig, Alfred E.
Taylor, A. E.
Thacher, J. S.
Thayer, W. S.
Thompson, W. Gilman
Tileston, W.
Tyson, Jas.
Vaughan, V. C.
Vickery, H. F.
Wadsworth, A. B.
Warthin, A. S.
Weaver, Geo. H.
Welch, Wm. H.
Wells, H. G.
Whipple, Geo. H.
White, F. W.
White, Wm.
Williams, H. U.
Wilson, Louis B.
Withington, Chas. F.
Wood, Edward J.
Wood, Francis C.
Woodyatt, R. T.

Tuesday, May 9

Morning Session.—The Association was called to order by President Sewall at 9.10 A.M., who delivered the President's address.

The Treasurer presented his annual report, showing receipts to have been $2475.44; expenditures, $2142.32; leaving a balance on hand of $333.12 in the treasury. The report was referred to an auditing committee composed of Drs. Reid Hunt and Richard P. Strong.

The Secretary presented the following recommendations from the Council:

Resolved, That for the ensuing year the annual dues shall be $5.00 for Laboratory Workers, $7.50 for Associate Members, and $15.00 for Practitioners. That the Transactions of the Association to Emeritus Members shall be $4.00 a volume.

The Council recommends that contributors to the Transactions be limited to 15 printed pages; an exception may be made by the Recorder in the case of invited guests, but in no case shall the time limit of October 15 be extended to accommodate invited but delinquent guests.

The Council recommends that the New York State Library, the Kansas City Medical Library, and the Vanderbilt School of Medicine be placed on the mailing list to receive the Transactions.

The Council also recommends the adoption of the following amendment to Article II of the Constitution, which is as follows:

Resolved, That Paragraph 2, Article II, of the Constitution be amended by inserting after the second paragraph the following:

Provided, That in case of removal of an active member to a locality so distant that his attendance at the annual meetings may reasonably be regarded as impossible, the Council may be empowered to transfer the name of such a member to the list of emeritus members, without regard to the length of his previous active membership.

(Signed). W. T. Longcope,
Joseph Sailer,
Reid Hunt,
E. L. Opie,
H. A. Christian.

The Council recommends that the following words be added: "during the period of his absence."

The Council recommends the election of the following officers, Honorary Members, Active and Associate Members:

President—George Dock.

Vice-President—Francis H. Williams.

Secretary—Thomas McCrae.

Recorder—Thomas R. Boggs.

Treasurer—J. P. Crozer Griffith.

Councillor—James B. Herrick.

Representative on the Executive Committee of the Congress of American Physicians and Surgeons—Theodore C. Janeway.

Alternate Representative—Richard P. Strong.

Honorary Members.—William C. Gorgas, Surgeon-General, U. S. A.; George M. Kober, Washington.

Active Members.—Charles C. Bass, New Orleans; Nellis B. Foster, New York; J. Ramsay Hunt, New York; James W. Jobling, Nashville; Howard T. Karsner, Cleveland; Francis W. Peabody, Boston; Peyton Rous, New York; Walter R. Steiner, Hartford; Albert E. Taussig, St. Louis; Rollin Turner Woodyatt, Chicago.

Associate Members.—Frederick M. Allen, New York; Alphonse R. Dochez, New York; Charles W. Edmunds, Ann Arbor; John H. Eyster, Madison, Wis.; Arthur D. Hirschfelder, Minneapolis; Arthur S. Loevenhart, Madison; Herman O. Mosenthal, Baltimore; Edward Carl Rosenow, Rochester; George C. Shattuck, Boston; Gerald B. Webb, Colorado Springs.

The "Symposium on Acidosis" was presented as follows: "Biochemistry of Acidosis," by Dr. Lawrence J. Henderson (by invitation); "Acidosis in Infants and Children," by Dr. John Howland; "Acidosis in Diabetes," by Dr. A. T. Woodyatt; "Acidosis in Acute and Chronic Diseases," by Dr. Channing Frothingham, Jr.; "Investigations in Diagnosis and Treatment," by Dr. L. G. Rowntree.

The discussion was opened by Dr. Yandell Henderson, by invitation, and participated in by Drs. Van Slyke, Meltzer, Janeway, Joslin, Hoover and Hare, and closed by Dr. Lawrence J. Henderson.

Drs. F. G. Novy and P. H. De Kruif presented a communication on "Anaphylatoxins," which was not discussed.

Drs. Fredk. P. Gay and H. T. Chickering presented a paper on "The Treatment of Typhoid Fever by Intravenous Injections of Sensitized Vaccine Sediment," which was discussed by Drs. Warfield and Miller, and closed by Dr. Gay.

Dr. C. P. Howard presented a communication on "The Physical Signs of Gunshot Wounds of the Chest," which was discussed by Dr. Riesman.

Dr. G. H. Whipple presented a paper on "Various Proteose Intoxications," which was not discussed.

Drs. H. R. M. Landis and F. A. Craig presented a paper on "The Food Problem in Dispensary Patients of Different Nationalities," which was discussed by Dr. Solis Cohen.

Adjourned at 12.30 P.M.

Wednesday, May 10

Morning Session.—The Association was called to order at 9.15 A.M., and the President appointed Drs. Fredk. T. Lord and Louis B. Wilson as tellers for the election of officers and members, and the following were elected:

President—George Dock.

Vice-President—Francis H. Williams

Secretary—Thomas McCrae.

Recorder—Thomas R. Boggs.

Treasurer—J. P. Crozer Griffith.

Councillor—James B. Herrick.

Representative on the Executive Committee of the Congress of American Physicians and Surgeons—Theodore C. Janeway.

Alternate Representative—Richard P. Strong.

Honorary Members—William C. Gorgas, George M. Kober

Active Members.—Charles C. Bass, New Orleans; Nellis B. Foster, New York; J. Ramsay Hunt, New York; James W. Jobling, Nashville; Howard T. Karsner, Cleveland; Francis W. Peabody, Boston; Peyton Rous, New York; Walter R. Steiner, Hartford; Albert E. Taussig, St. Louis; Rollin Turner Woodyatt, Chicago.

Associate Members.—Frederick M. Allen, New York; Alphonse R. Dochez, New York; Charles W. Edmunds, Ann Arbor; John H. Eyster, Madison, Wis.; Arthur D. Hirschfelder, Minneapolis; Arthur S. Loevenhart, Madison; Herman O. Mosenthal, Baltimore; Edward Carl

Rosenow, Rochester; George C. Shattuck, Boston; Gerald B. Webb, Colorado Springs.

The following amendment to Paragraph 2, Article II, of the Constitution was unanimously adopted: Insert after the second paragraph the following:

Provided, That in case of removal of an active member to a locality so distant that his attendance at the annual meetings may reasonably be regarded as impossible, the Council may be empowered, should it so desire, to transfer the name of such a member during his absence to the list of emeritus members without regard to the length of his previous active membership.

Dr. James Tyson, chairman of the Committee on Subscriptions to the George Washington Memorial Building Fund, reported receipts in cash to date, $50, a grand total of $452. In view of the discouraging results, the committee recommends that the Association should place on the project the seal of approval or the reverse and also suggests the appointment of an entirely new committee if the project is to be continued.

Dr. Frank Billings moved that the Association recommends to the Executive Committee of the Congress of American Physicians and Surgeons that a joint committee consisting of a representative from each constituent society be created for the purpose of promoting and securing funds for the erection of the George Washington Memorial Building for a permanent home for the national scientific societies, and that Dr. George M. Kober be designated to represent this Association on such a committee and to present this matter to the Executive Committee of the Congress of American Physicians and Surgeons. Carried.

Dr. Reid Hunt, for the Auditing Committee, reported that the accounts of the Treasurer had been examined and found correct.

Dr. E. J. Wood presented a paper on "The Etiology of Pellagra," which was discussed by Drs. Jos. Sailer and Nathan E. Brill, and the discussion was closed by Dr. Wood.

Dr. Wm. Charles White presented a contribution on "Lipase in the Urine of the Tuberculous." No discussion.

Drs. C. H. Bunting and J. L. Yates presented a paper on "Leukemia, Lymphosarcoma, and Hodgkin's Disease," which was discussed by Drs. Wells, Janeway, Billings, and the discussion closed by Dr. Bunting.

Drs. W. T. Longcope and F. A. Rackeman presented a paper on "Renal Function in Serum Disease." No discussion.

Drs. Lawrason Brown, S. A. Petroff, and F. H. Heise presented a paper entitled "The Occurrence of Living Tubercle Bacilli in a River Contaminated with Sewage from a Health Resort." No discussion.

Dr. Joseph Sailer presented a communication on "Polycythemia Treated with Radium," which was discussed by Dr. Einhorn.

Dr. H. C. Giffin presented a paper entitled "The Results of the Treatment of Pernicious Anemia by Transfusion and Splenectomy." Dr. M. A. Blankenhorn (by invitation) presented a communication on "The Bile Content of the Blood in Pernicious Anemia," and Dr. C. F. Hoover and M. A. Blankenhorn presented a paper on "Dissociation Icterus."

These papers were discussed by Drs. Rowntree, Whipple, and Cabot, and the discussion was closed by Drs. Giffin, Blankenhorn, and Hoover.

Drs. E. E. Southard and M. M. Canavan presented a communication on "The Anatomical Approaches to the Problem of the Functional Psychoses, Including a Particular Study of Five Brains" (illustrated with lantern slides), which was not discussed.

Drs. Julius Friedenwald and F. H. Baetjer presented a paper on "Roentgen-ray Diagnosis of Gastric Ulcer," which was discussed by Dr. Franklin W. White, and the discussion was closed by Dr. Friedenwald.

Dr. A. E. Taussig presented a paper on "Some Blood-pressure Phenomena in Exophthalmic Goiter;" Dr. H. S. Plummer presented a communication on "The Function of the Thyroid—Normal and Abnormal;" Dr. E. C. Kendall (by invitation) presented "Studies of the Active Constituent, in Crystalline Form, of the Thyroid;" Dr. Louis B. Wilson presented a communication on "The Pathologic Changes in the Sympathetic System in Goiter," which was illustrated with lantern slides; Dr. W. B. Cannon presented a communication, illustrated with lantern slides, on "Some Conditions Affecting Thyroid Secretion." The papers on the symposium on goiter were not discussed.

Dr. A. S. Warthin presented a paper entitled "Pancreatic Changes in Latent Syphilis," which was illustrated with lantern slides. No discussion.

Dr. C. C. Bass presented a communication on "The Control of Malaria by Malaria Carriers," illustrated with lantern slides, which was discussed by Dr. Cabot, and the discussion closed by Dr. Bass.

Dr. W. M. Coplin presented a communication on "Unilateral Renal Hypoplasia and Dysplasia; Relation to So-called Hypogenetic Nephritis;" illustrated with lantern slides of macroscopic and microscopic photographs, and by specimens. No discussion.

Dr. C. M. Montgomery, by invitation, presented a joint communication with Dr. George W. Norris on "Physical Signs in Relation to Pulmonary Disease," illustrated with lantern slides, which was discussed by Dr. Norris.

Adjourned 1 P.M.

Wednesday, May 10

Evening Session.—Dr. Louis Hamman presented a communication on "Blood-sugar Estimations as a Test of Carbohydrate Tolerance," illustrated with lantern slides. No discussion.

Drs. H. K. Detweiler and W. L. Robinson (by invitation) presented a communication on "Experimental Endocarditis, its Production with Streptococcus Viridans of Low Virulence," illustrated with lantern slides, which was not discussed.

Dr. Thomas Ordway presented a paper on "Remissions in Leukemia Successfully Produced by Radium in Cases Completely Resistant to X-ray and Benzol Treatments" (illustrated with lantern slides), which was discussed by Drs. Sewall and McPhedran, and the discussion closed by Dr. Ordway.

Drs. C. F. Martin and E. H. Mason presented a communication on "Observations on the Starvation Treatment of Diabetes" (illustrated with lantern slides), which was discussed by Drs. Jacobi, Martin, Meltzer, Van Slyke, and Fussell.

Drs. John A. Kolmer and S. Solis-Cohen presented a "Preliminary Note on the Germicidal Action of Quinine Salts and Allied Compounds upon Pneumococcus Cultures" (illustrated with lantern slides), which was discussed by Drs. Novy, Kolmer, and the discussion closed by Dr. Solis Cohen.

Thursday, May 11

Morning Session (9 A.M.).—Dr. Max Einhorn read a paper on "Gastrohydrorrhea in Cirrhosis of the liver, Accompanied by Pyloric Stenosis," which was discussed by Drs. Sewall, Christian, and the discussion closed by Dr. Einhorn.

Dr. James Alexander Miller presented a communication on "The Effects of Exposure to Cold upon Experimental Infection of the Respiratory Tract," which was discussed by Drs. Sewall and Meltzer.

Dr. Warren Coleman read a paper on "The Expectorant Action of Ammonium Chloride," which was discussed by Dr. Jacobi, Meltzer, Erlanger, Rowntree, Einhorn, and the discussion closed by Dr. Coleman.

Drs. J. M. Anders and George H. Meeker presented a communication on "The Coagulation Time in Lobar Pneumonia, with Statistics and a Preliminary Experimental Study of the Coagulation Process," which was discussed by Drs. Meltzer, Cole, Sewall, Einhorn, and the discussion closed by Dr. Anders.

Dr. Henry A. Christian presented a "Study of the Action of Certain Diuretics in Chronic Nephritis," which was discussed by Drs. Thayer, Anders, Rowntree, and the discussion closed by Dr. Christian.

Drs. A. W. Hewlett, Gilbert, and Wichett presented a communication on "The Toxic Effects of Urea on Normal Individuals," which was discussed by Drs. Meltzer, Coleman, Christian, Bond, Rowntree, and the discussion closed by Dr. Hewlett.

Drs. Peyton Rous and O. H. Robertson presented a communication

entitled "Factors in Normal Blood Destruction," which was discussed by Dr. Meltzer, and the discussion closed by Dr. Rous.

Dr. Thomas R. Brown presented a communication entitled "Observations on Intestinal Auto-intoxication, Especially as Regards the Specificity of Toxin," which was not discussed.

Dr. Ralph Pemberton presented a paper entitled "Observations on the Metabolism and Treatment of Rheumatoid Arthritis," which was not discussed.

Drs. Francis W. Peabody and John A. Wentworth presented a communication on "The Vital Capacity of the Lung and its Relation to Dyspnea in Heart Disease," which was discussed by Dr. Sewall, and the discussion closed by Dr. Peabody.

Dr. M. J. Couret presented a joint communication, with Dr. C. W. Duval, on "The Immunizing Effect on Swine of Desiccated Sensitized Hog Cholera Virus," which was not discussed.

Dr. David I. Macht (by invitation) presented a communication on "The Action of Opium Alkaloids and their Combinations on the Vomiting Center," which was discussed by Dr. Babcock, and the discussion closed by Dr. Macht.

Dr. Paul D. Lamson presented a communication on "The Role of the Liver in Acute Polycythemia," which was discussed by Dr. Sewall, and the discussion closed by Dr. Lamson.

Upon motion of Dr. Hoover a rising vote of thanks was given to President Sewall for the able administration of his office and for the excellent program presented at the meeting; and to the retiring Secretary, Dr. Kober, for the admirable arrangements for the session of the Association and for his faithful work as Secretary for a period of eight years.

The following papers were read by Title:

"Studies in Syphilis of the Stomach; its Diagnosis and Prognosis," by Dr. Franklin W. White.

"Studies in Immunity to Poliomyelitis," by Dr. M. J. Rosenau.

"Some General Considerations Concerning the Affections of the Valves of the Heart," by Dr. E. Libman.

"Observations upon Cases of Purulent Pericarditis, with Special Reference to Pericardiotomy," by Drs. C. N. B. Camac and Eugene H. Pool.

"Treatment of Migraine," by Dr. B. K. Rachford.

Adjourned 12.15 P.M.

GEORGE M. KOBER,
Secretary.

ADDRESS OF THE PRESIDENT

SCIENCE THE CONSERVATOR OF TRUTH

By HENRY SEWALL, M.D.
DENVER

An association of physicians in the popular sense would likely signify a collection of persons whose time and energies are devoted wholly to attendance upon the sick, and among whom intercourse might be limited to discussion of the practical details of the clinical diagnosis and treatment of disease. Such restrictions must surely reduce medicine to empiricism, and its practice to a mechanical art of rather low order. Our founders held a broader view. They conceived medical practice as a superstructure of shifting design upborne upon foundations which are continually being broadened, deepened, strengthened, and renewed.

They realized that the art of medicine can only achieve its ideal through the exact application of laws of matter and life which the physical chemist, the physiologist, pathologist, and psychologist have laboriously beaten out upon the anvil of experiment. They had the high purpose, unless I err, of bringing together and strengthening by union a congregation of some of those, from whatever field of labor, whose dominant purpose in life is the advancement of medical knowledge.

The records and influence of this Association seem not unworthy of the ideals of its founders. But to say that we still live is but to admit that we still strive, and I submit that our best destiny cannot be grasped unless we continually seek to cast out weakness and lay on strength.

There are privileges internal and obligations external. Looking within our ranks, can it be doubted that a great fund of potential energy remains inactivated through lack of intimate social intercourse? The internal benefits of this Society could not but be enhanced were each member to strive to enlarge his circle of intimates and seek a broader intercourse, especially with those recently entering the ranks.

Looking outward, it seems to me that the Association of American Physicians has relations to the community not comprehended in its volumes of TRANSACTIONS. This body might very properly, perhaps, in a quasi-judicial capacity, pass upon public questions the data of which belong to scientific medicine, when its pronouncement would obviously benefit the community. An appropriate present issue would seem to be an encouragement of the plan to unify the requirements for medical practice throughout the United States as it has recently been embodied in the establishment of a National Board of Medical Examiners. It is to be hoped that the self-devotion of Rodman will be witnessed by his works.

Such an exercise of privilege should, of course, be used only with such consummate tact as would with certainty avoid both polemics and politics.

One practical word, also, with regard to the construction of the TRANSACTIONS of the Association. It would appear that when papers are long and to be printed fully in the current literature, it were better to present them to the Recorder in the form of abstracts rather than unduly retard the publication of the annual volume.

Death has made a heavy charge upon the personnel of the Association during the past year. Five members of long standing have ceased their work; F. A. Delafield, G. M. Sternberg, E. L. Trudeau, A. A. Smith and S. B. Ward. All were among the Founders of the Association. The first three were Honorary Members, the last two were on the Emeritus list. Further words were vain.

In casting about for a message I might bring you worthy of the single opportunity which life can offer, one cradle-familiar theme insistently forced itself into the foreground; it is, Science, Preserver of the Spirit of Truth. Human emergency is the opportunity of platitude.

To one who stands aloof and views the madding crowd, a single mainspring of action is most in evidence—self-interest. Or, where the struggle for material aggrandizement is replaced by an idea, we witness the best-intentioned men ruthlessly pursuing vagaries of beliefs whose doctrines are as various as the environments from which they spring. Men strive to accomplish a purpose, by hook or by crook, if need be, and all their actions reflect the point of view. The commercial agent exploits the virtues of his goods, not with the prime motive to tell the truth, but to get your money. The plea of an advocate in a court of justice seeks but the accomplishment of some ulterior design. The stirring editorial may be penned by one who secretly scouts his published tenets. The capacity to do fine writing seems itself often an irresistible temptation to pervert the spirit of truth for the glamor of sensational impression.

In the scenario of the moving picture it is impossible to distinguish the true from the faked. So, too, in the scenario of life the puppets move and group themselves to secure effects with no regard to abstract verities.

Self-interest, expediency, ulterior motives, preconceptions, these are the springs of action and of thought. The curbstone psychologist who has become adept in calculating the course of human will under the driving forces of appetite and ambition has an egregious advantage in the struggle for social aggrandizement.

It seems, indeed, as if there were no such thing as an axiom to which all men must subscribe. No amount of evidence can convince of error the "anti" who hugs the belief that he or she is upholding a moral principle. A great group of people is bound by the dogma that the unwelcome facts of life may be abolished by ignoring them; still, with naïve but sardonic humor, these brothers and sisters have chosen the title of "scientists." Well-meaning sects, like fluorescent matter, appropriate certain rays and claim their glow to comprise all light. In times of war whole nations draw opposite conclusions from the self-same facts; belief and will are strictly shaped by the training under which the mind develops.

Truth is rather the luxury than the necessity of civilized mankind, and where unwelcome it can rarely overthrow the pleasing falsehood.

As we review the orders of society there are now but scant signs of that obsolescent chivalry in which personal truthfulness was guarded as the very apple of its eye. Were the self-devotion which today leads men to slaughter on the battlefield transformed to the purposes of peace, what a force for social progress would there be!

A real but insidious menace confronts our race, increasing in energy proportional to the intensity of competition in life. The children of each generation seem less and less imbued with thought of and respect for Truth as an ultimate good.

If these are indeed facts, it is high time that we take account of the situation and consider measures for its relief.

When there is human need we go into committee of the whole and fix upon some small group of men who by talents and disposition would seem best qualified to suggest a remedy. When we look about for men most likely to be concerned in the preservation of the Spirit of Truth we naturally turn to those professions in which altruism is the dominant impulse, and as such the callings of the physician and of the minister of religion take first rank. An unbiased estimate of these vocations cannot but disclose that truth is not the absorbing end of activity, however cultivated as a means of securing preconceived desires. The vogue of the physician depends less upon what he is than on what is thought he is. His finest intentions may reach their aim through unwitting diffusion of false impressions. Hippocrates and Charaka themselves appear to have enjoined upon their disciples much in the way of demeanor, little of character.

With no desire to offend, it must be asserted that the religionist, as such, is the least dependable of all the allies of concrete truth. The dearest foe of the student of Nature is the human tendency to unquestioning faith in desired beliefs.

Where, then, shall we turn for a priest of the Spirit of Truth? Where, indeed, but to the scientific investigator? To him alone Truth is the all-desirable, and stands not only as a means but as the end of his designs. He alone is loyal servant to the stern discipline that bids him slay the erring children of his intellect upon the altar of his devotion.

Truth itself demands that we seek the limitations of this apotheosis of science. Science has no intentioned concern with human love, but to faith, hope and charity it may add truth. As Welch has said, "Nature is neither kind nor cruel, but simply obedient to law;" still, also, we must admit, with Matthew Arnold, that there is "an enduring power, not ourselves, which makes for righteousness."

The seeker of truth must live in an atmosphere of pure desire but such a character were futile without the arduous scientific training that holds the imagination to the stepping-stones of fact.

In this brief sketch it is not expedient to analyze the resources of knowledge to determine what proximate principles are best adapted to sustain the spirit of truth. It is dogmatically asserted that so-called pure science, something inadequate to human appetite and digestion, is the indispensable servitor of truth. And, for substantial reasons, biological research is probably the choicest field for the cultivation of the talents of truthfulness.

We were all brought up, perhaps, with a conception of science as a ruthless machine for the shackling of human emotion and imagination, but none can now gainsay that science as the method for establishing truth includes a wider range of human activity than the wildest imagination could have conceived a little while ago. The boldest Shakespearian fancy of three centuries back has become the staple of the electrical utility corporation of today.

The very words "matter" and "energy" now suggest such a vortex of eerie conceptions that, could they have been foreshadowed in fiction two generations gone, would have branded their author a lunatic. In his little book *The Fitness of the Environment*, L. J. Henderson has given the data from which he who wills may well-nigh construct in imagination a new world whose vital and physical reactions would perform upon a plane of irritability in which what we now know as Nature would be completely transformed.

Art and the humanities can lose nothing but must gain immeasurably from the pursuit of science.

One writer puts it, "The whole duty of Art is listening for the voice of God." Ruskin said, "nothing can be beautiful which is not first true." The Apocrypha declares, "The more thou searchest, the more thou shalt wonder."

Man descended from the angels is a dismal failure; man arisen from the brutes is a glorious success.

Can anything be finer than a scheme to coördinate the forces of mankind toward conscious evolution, and can it be accomplished except through sway of the spirit of truth?

This is a crude and inadequate sketch of what appear to be real conditions and I would fain save it from the limbo of precious platitudes.

My major premise is that devotion to truth is becoming lost to the peoples by lack of reverence and insensibility to its potency.

My minor premise is that there exists ready at hand a cult whose sole reason for existence is magnification and clarification of the great principle, the cult of the scientific investigator.

My conclusion is that a remedy may be found if in our schemes of education in school and college and elsewhere a fundamental object should be to create an atmosphere whose active component is truth; and to inculcate the knowledge that this indeed is the vital principle.

He who is personally engaged in original research well understands that the one countersign to success is "verity," but the vast and careless majority needs a system of special cultivation. Happy are those undergraduate students who have the privilege of mingling with workers of riper training who are devoting their first elective years to original investigation. Such a body induces a mental and moral environment which is prone to direct for good the functions of all who dwell in it.

Even where conditions for instruction are less favorable, it is imperative that the teacher should tax his ingenuity to give the student, as may be done, the point of view of the investigator, and thus the simplest and most diverse problems may yield the joy of discovery, and, what is far more important, there will inevitably develop an intuition by which all the varied phases of life are tested, and, when the will is good, truth will rule mind and conduct.

ACIDOSIS IN INFANCY AND CHILDHOOD

By JOHN HOWLAND, M.D.
BALTIMORE

Acidosis in infancy and childhood is a frequent condition and an important one. It is dangerous and difficult to cure, but there is one favorable aspect to the therapeutics of acidosis in childhood which is that acidosis in the young is frequently a complication of acute self-limited disease. When the acidosis has been overcome there is the possibility of complete cure. We are not often compelled, after overcoming the acidosis, to treat chronic disease and always with the fear that acidosis will again arise. Chronic nephritis and diabetes which play the preponderant part in producing acidosis in adult life are relatively infrequent causes of acidosis in childhood.

By acidosis is meant not the mere appearance of the acetone bodies in the urine by qualitative tests. There is meant a demonstrable alteration in the acid base equilibrium coincident with a diminution in the alkali reserve of the blood and other tissue fluids. Were we to diagnosticate acidosis from acetone tests of the urine alone and rely for diagnosis upon the information which these give, we would reduce diagnosis in childhood to very simple terms, for more than 50 per cent. of children with febrile diseases pass urine giving this test. Acidosis would then be the most common disease in the calendar and the newspaper statements of last winter concerning epidemics of acidosis would be justified. But the diagnosis by qualitative tests is unjustified. The smallest number of infants and children with acetone bodies in the urine have a disturbance of the acid base equilibrium and what is equally important, the most frequent and severe forms of acidosis are not accompanied by acetonuria.

The clinical evidence of acidosis is hyperpnea; other than this there are no symptoms that are of much assistance in the diagnosis of acidosis. In the course of certain diseases of which it is a frequent complication, we may suspect its presence but we cannot prove it without hyperpnea or laboratory tests.

The laboratory tests of acidosis have been greatly developed in the last few years—one might almost say months. The most important are the determination of the carbon dioxide tension of the alveolar air, the determination of the hydrogen ion concentration of the blood, and the various methods for demonstrating the diminution of the alkali reserve such as van Slyke's method which measures the carbon dioxide of the plasma; Marriott's, which estimates the effective alkali reserve, and Sellards's, which shows a diminution of the bicarbonate of the serum.

One reason for the readiness with which young children develop acidosis is that they have a somewhat lower alkali reserve than the older child or adult, and this allows more readily a disturbance of the acid base equilibrium. There seems to be no doubt of this. The carbon dioxide of the plasma as shown by van Slyke's method is with children so low that with an adult it would indicate mild acidosis, and Marriott's method for determining the effective alkali reserve gives information which forces one to the same conclusion. Another reason is found in the readiness with which acetone bodies develop in the young from apparently insignificant and, indeed oftentimes, from undiscoverable causes.

We may roughly divide acidosis into that form which is due and those forms which are not due to the formation of the acetone bodies in great excess. These substances in either case may be excreted in the urine. For this reason qualitative tests of the urine alone prove nothing. Determinations of the amount present in the blood give the exact information required. In health the child has in the blood from 1 to 5 mgs. of the acetone bodies per 100 gms. of blood. With the onset of disease of any kind, a ten- to twentyfold increase frequently occurs. With many acute febrile diseases we find 20 to 40 mgs. But when the accumulation is such as to give the clinical and laboratory evidences of acidosis, the amount may be nearly 200 mgs., as much as is found with diabetic coma

which, of course, occurs with children but to which I shall make no further allusion here as it is not peculiar to childhood.

It has long been recognized that recurrent vomiting is frequently associated with an excessive formation of acetone bodies that appear coincidently with the vomiting. In perhaps the majority of instances, however, these bodies appear only after several days, and are in such cases to be considered the result of starvation. But in addition to recurrent vomiting, we must also recognize, and chemical studies have proved, that there occurs, in young children especially, an acidosis due to the very rapid and excessive production of acetone bodies; that this is not necessarily accompanied by vomiting or fever and that it appears without any discoverable cause. It does not depend upon starvation, for it is seen after proper and sufficient food. A number of these attacks have been studied by the methods at present available. It is clear enough that acetone body acidosis is present, but what determines the onset is entirely obscure. Death may result. Prompt, vigorous treatment, however, offers a better prospect of cure than with any other form of acidosis. The onset of the attack is sudden. The termination is likely to occur as suddenly. The disturbance, whatever it is that produces the attack, is not long lived and with its cessation it is usual for convalescence promptly to begin.

Of those forms of acidosis that are not due to the acetone bodies, the most frequent is the acidosis that occurs with severe diarrheal disease not of the ileocolitis type, the serious forms of the so-called summer diarrhea and cholera infantum. The majority of cases of diarrhea in infancy probably do not have acidosis. But a considerable number of infants with profuse diarrhea do develop acidosis, and the overwhelming majority of these die. To a very critical disease a most severe complication is added. The onset of acidosis is marked by hyperpnea usually with distinct nervous symptoms, great restlessness, alternating with stupor and eventually coma. The symptoms of acidosis may, by appropriate treatment, be overcome, we may renew the alkali reserve, but death usually results. Normal processes that are necessary for life may have been permanently inhibited, or abnormal processes that are incompatible with life may have been set in motion. In any event the

equilibrium with which life is possible is restored in but few cases. It is only when the acidosis is recognized early and overcome at once and there is prospect of cure.

It is very plain from quantitative estimation of the acetone bodies in the blood that they are not responsible for this form of acidosis. Upon what then may it depend? There is one feature of the disease in its severe forms that is striking. There is usually nearly complete anuria. With the failure of the different kidney functions under such circumstances there is included the failure of the acid-excreting function, one of the most important. The body can no longer rid itself of the acid end-products of metabolism by the excretion of acid phosphate. This is held back disturbing more and more the acid base equilibrium. This is one possibility. Another is an accumulation of lactic acid. Still a third is loss of base by the bowel. That an excess of sodium is lost in the stools is undoubted. But it has not been proved that the sodium is in a potentially active form. It may be only in a neutral salt such as sodium chloride. It will require further study to determine the factors that are responsible for this fatal complication of diarrhea.

With nephritis in children, acidosis may develop just as it does in the adult, though it seems to be rather more common with acute nephritis on account of the relative rarity of chronic nephritis and the prevalence of infectious disease among the young. In such cases there is no acetonemia. The suggestion has been made by several writers that the acidosis is due to the loss of the acid-eliminating function of the kidney and the consequent retention of acid phosphate in the blood. If such were the case, one should find an excess of inorganic phosphate in the serum. This Marriott and I have been able to do. Under normal circumstances the inorganic phosphorus content of the serum is but 1 to 3 mgs. in each 100 c.c. of serum. With nephritis there is a moderate increase, as a rule, though even with fatal nephritis the amount may be within normal limits. But when acidosis develops in nephritis we have found an increase of from five to fifteen times the normal. The constant retention of a small amount of acid phosphate would gradually rob the body of alkali and would eventually disturb the acid base equilibrium. Alkali treatment renews the alkali reserve but

apparently does not markedly reduce the phosphate. Indeed we have found in some instances a progressive increase in the amount of phosphate but not of sodium chloride. The retention seems at least at times to be a specific one.

Another condition with which acidosis may develop is severe burns. Blackfan has determined its presence in three recent cases. In all the grade of the acidosis was severe enough to threaten life. With appropriate treatment the acidosis was overcome not to return, though two of the patients subsequently died as a result of the burns.

In the course of pneumonia, acidosis may occur. It brings about a distinct alteration in the character of the respiration. Rapid, panting respirations become slower and deep and exaggerated. This complication of pneumonia is infrequent and the cause is quite unknown. Similarly, in the course of other diseases, this disturbance may arise, not often enough to make any clear particular etiological relationship, but nevertheless with sufficient frequency to make acidosis a condition constantly to be borne in mind when treating either acute or chronic disease in the child. And the recognition of acidosis has a very important practical bearing. Its early rational treatment may be the means of saving life.

ACIDOSIS IN DIABETES

By R. T. WOODYATT, M.D.
CHICAGO

As a basis for the discussion of acidosis occurring in diabetic individuals, I will first develop certain views as to the respects in which a diabetic differs from a non-diabetic individual and then return to the subject proper.

THE ABSENCE OF A SHARP LINE OF DIVISION BETWEEN DIABETIC AND NON-DIABETIC STATES

In the normal individual there exists a proportionality between the rate at which glucose is utilized or stored, and the rate at which it is excreted unchanged in the urine. This proportionality differs with different rates of glucose supply to the cells. When the rate at which glucose is brought into the tissues from both external and metabolic sources is below a certain minimum (expressed in terms of the weight of glucose per unit weight of tissue and unit of time) nearly all the glucose is utilized or stored and only a trace escapes in the urine unchanged. When the rate of glucose supply to the cells (from both external and internal sources) is above this minimum then the percentage of wastage increases rapidly. And when the rate of supply rises above some $3\frac{1}{2}$ grams per kilo per hour, as it can be made to do by intravenous administrations, then in a normal well-nourished individual, 35 to 50 per cent. may be excreted.[1]

Under these conditions a normal individual is, as it were, 35 to 50 per cent. diabetic, and he has intense glycosuria, polyuria, and

[1] Statements based on studies with sustained intravenous injections of sugars carried out by Sansum, Wilder and Woodyatt, 1915–16, in part unpublished.

thirst like those of a genuine case of diabetes with a lower rate of glucose supply.

In cases of so-called "total" human diabetes there also exists a proportionality between the rate at which glucose is stored or utilized, and the rate at which it escapes in the urine. And as in health, this proportionality varies with the rate of glucose supply to the cells (the grade of the diabetes and other factors remaining the same). If the rate of supply is below a certain minimum, then, as in health, most of the glucose supplied is stored or utilized and only a trace appears in the urine. The so-called "total" diabetic differs from the normal only in that this minimum is absolutely lower than in health. In order to reduce the rate of glucose supply to the cells below the minimum necessary to make a case of "total" diabetes free from glycosuria, it is necessary to stop entirely all intake of sugar-forming elements in the form of food and also to cut down the rate of endogenous glucose formation. This means fasting and rest with the exclusion of cold and every other influence which may stimulate metabolism. But fasting, rest and warmth do not wholly stop the endogenous formation of glucose. They only decrease it. As Lusk has pointed out, during a fast glycogen reaccumulates in dogs which have previously been deglycogenized by the use of phlorhizin plus cold or epinephrin, a fact we have several times confirmed. In such cases the glycogen comes for the most part from the protein metabolism which persists in fasting. Yet uncomplicated cases of "total" human diabetes become non-glycosuric during a fast in spite of this endogenous glucose supply. Cases of severe diabetes rendered non-glycosuric by fasting, rest and warmth lose all the ordinary symptoms of diabetes, even the respiratory quotient rising to a degree suggesting some glucose utilization, as shown by Benedict and Joslin and by Du Bois.

It is accordingly clear that the state of every normal individual becomes diabetic when the rate of glucose supply to the cells is high enough, and every case of human diabetes passes into the non-diabetic state when it is possible to make the rate of glucose supply to the cells low enough. The difference between a "total" diabetic, so-called, and a healthy person is purely quantitative.

ACIDOSIS IN GENERAL

Returning now to the subject of the acidosis, I would emphasize the point that acidosis in diabetes occurs under the same fundamental conditions and conforms to the same general laws which pertain to acidosis in non-diabetic individuals. That particular type of acidosis which is so commonly seen in the severer cases of diabetes, the type characterized by the appearance in the blood and urine of betaketo- and betahydroxybutyric acids and acetone might appear to have laws of its own and to differ specifically from the same type of acidosis when seen in non-diabetics during the course of simple fasting or a one-sided diet, but the difference is only a matter of degree.

Our knowledge of diabetic acidosis began with Hallervorden's discovery of increased quantities of ammonia in the urine of cases of severer diabetes. Previous experimental studies by Hallervorden and Coranda having demonstrated that an increase of urinary ammonia was commonly associated with an increased excretion of acid radicals, it was suspected that this might be the case in diabetes, and following this idea that the increase of urinary ammonia might signify an increased excretion of ammonium salts of unknown acids, Stadelman and Hallervorden proved that large quantities of alpha crotonic acid could be distilled from acidified diabetic urine—this acid arising from the decomposition of *l*-betahydroxybutyric acid, as was later shown by the works of Külz and of Minkowski. It was to this condition that the term *acidosis* was first applied and in this paper, for the sake of convenience, the term will be used in this original sense, although it is clearly recognized that an increased production and excretion of acid radicals is not inevitably associated with an increased hydrogen ion concentration in the blood, nor a depletion of the blood bicarbonate, because if the body is adequately supplied with suitable bases during the course of the acidogenic process, these latter phenomena need not develop.

ORIGIN OF THE ACIDOSIS COMPOUNDS

It is at present common knowledge that betahydroxybutyric acid and its two congeners betaketobutyric acid and acetone, known collec-

tively as the "acidosis compounds" or "acidosis bodies," in accordance with Naunyn's suggestion and less aptly as the "acetone bodies" after Geelmuyden, arise from products formed in the catabolism of fats and proteins and more specifically from certain of the lower fatty acids containing an even number of carbon atoms, in particular perhaps from butyric acid. The chemistry of the formation of these lower fatty acids from the higher fatty acids and from certain of the amino acids—as well as the mechanism by which they are converted into the acidosis compounds—cannot be here discussed.

CONDITIONS FAVORING THEIR APPEARANCE

It has long been known that one fundamental prerequisite for the accumulation in the tissues and subsequent excretion of abnormally great quantities of the acidosis compounds is a relative diminution in the rate of carbohydrate utilization. When for any reason whatsoever that rate at which glucose is utilized in the body falls below a certain minimum relative to the rate of the fat and protein catabolisms, then the acidosis compounds appear in the blood and urine. It is worthy of emphasis that when we speak of a decreased rate of carbohydrate utilization in this connection, we should have in mind specifically the catabolism of *glucose*, and think not merely of an *absolutely* decreased rate of glucose catabolism, but of a diminution *relative* to the existing rate of lower fatty acid (for instance, butyric acid) oxidation.

In 1914 Zeller[1] fed patients isocaloric, non-protein diets. He varied the proportions of fat and carbohydrate and first noted an increased output of ammonia when the proportion of carbohydrate was less than one part by weight to four parts by weight of fat. He reckoned that for the complete utilization of two molecules of the particular fat which he employed, at least one molecule of glucose must oxidize at the same time. Lusk suggests re-reckoning these results somewhat as follows: Two molecules of fat can yield by saponification six molecules of fatty acid and two of glycerol. The two molecules of glycerol can yield in the body one molecule of glucose. Adding this to the glucose derived from the diet directly, it would

[1] Arch. f. Physiol., 1914, p. 213.

appear if we accept Zeller's results (and leave out of consideration for the moment the protein metabolism) that six molecules of higher fatty acid required for their complete oxidation the simultaneous utilization of at least two molecules of glucose. One might accordingly say: *When the mixture of metabolites oxidizing in the body contains more than three molecules of higher fatty acid to one of glucose, then the body "smokes" with acidosis compounds like an automobile with too much oil in the cylinders.* It is to be expected that some equally definite but not identical relationship exists between the number of glucose molecules necessary for the complete utilization of such immediate precursors of the acidosis compounds, as for example, butyric acid (possibly 1 glucose molecule for 10 to 12 butyric acid molecules?).

ACIDOSIS IN FASTING

Now when an individual fasts, his cells naturally continue to oxidize foods. Before the fasting begins the proportions of fat and carbohydrate catabolized are determined roughly by the proportions of fat and carbohydrate in the diet supplied from the outside world. After fasting begins the proportions of fat and carbohydrate catabolized must be fixed more by the proportions in which these stuffs are present in the tissues themselves. The cells will be fed with what there is and the proportions in which they catabolize carbohydrate and fat must depend in the end upon the proportions in which these stuffs have been stored. R. M. Lang[1] in Glasgow, has confirmed these principles by direct experimental studies.

It is accordingly clear how, with respect to acidosis, fasting may produce a variety of effects in different individuals, depending upon how their bodies may assay for fat and glycogen at the time fasting begins, and this must depend to a large extent on the previous diet. An individual in whom there is no appreciable fat and only a trace of glycogen will, during a fast, necessarily subsist almost wholly on body protein. It is very doubtful whether this is productive of

[1] Biochemical Journal, 1915, ix, 456–478.

any acidosis of the type we are discussing because 45 to 58 per cent. of the protein is capable of conversion into glucose and of the remaining 55 to 42 per cent. only a fraction consists of ketogenic amino acids, *i. e.*, of amino acids capable of yielding acidosis compounds. Unless something interferes with the oxidation of the glucose derivable from protein, this glucose probably suffices for the complete oxidation of the ketogenic fraction of protein. This also is in harmony with the results of Lang's experiments. On the other hand, if an individual at the beginning of a fast contains a considerable glycogen reserve and also a normal amount of fat, we would expect at first no significant acidosis but later, as the glycogen reserves become depleted sooner than the fat reserves, we should expect an increasing preponderance of fat in the metabolism and hence a rising acidosis. If the fasting were pushed until the fat reserves were themselves sufficiently depleted, one might then expect again a decline of the acidosis as the metabolism reverted to the protein type. Again, if an individual at the beginning of a fast contained an excess of fat in proportion to the glycogen, one might expect a quicker and higher acidosis during starvation than in a strictly normal person. Perhaps the sudden and sharp fasting acidosis observed by Folin in the obese is due in part to the fact that these persons thrown back upon a diet consisting of their own tissue materials find them excessively fatty.

ACIDOSIS IN DIABETES

Acidosis develops in diabetics under exactly the same fundamental conditions which cause acidosis in non-diabetics. But in diabetes, owing to pancreatic insufficiency, the maximum rate at which glucose can be oxidized in the body is fixed at some level which is absolutely lower than in health. The limited amount of glucose which the diabetic can oxidize per kilogram of body weight per unit of time fixes the amount of fat which he can oxidize without developing acidosis during the same time. He can only burn about four times as much fat as carbohydrate without acidosis. It therefore so happens that in the severer cases of diabetes a rate of fatty acid metabolism, which in the absolute sense is not greater than what

might occur in health, becomes excessive in proportion to the amount of oxidizing glucose, and so acidosis develops.

In order to check a diabetic acidosis it is necessary to restore the proper ratio of fatty acid to glucose oxidation by bending down the fatty acid metabolism to whatever level is fixed by the existing rate at which glucose is oxidizing. In diabetes protein alone, if metabolized in sufficient amounts, may be productive of acidosis as well as fat because, although protein in breaking down liberates plenty of glucose for the complete oxidation of its own ketogenic fraction, in diabetes there is a limited rate at which the glucose can burn. Accordingly, to check a diabetic acidosis it is necessary to reduce both the protein and the fat metabolisms. Fasting, rest and warmth accomplish this and we might expect such a procedure to diminish acidosis in many cases of diabetes just as the same treatment causes a cessation of glycosuria. The old observation that it usually does so is verified by the recent studies of Allen and of Stillman and Van Slyke. It would not be expected, however, that in diabetics, any more than in non-diabetics, fasting would always have exactly the same effect with respect to acidosis. We would always have to consider what the previous diet of the diabetic had been and how his body would analyze for fat and glycogen at the beginning of the fast, taking account not merely of the fat or the glycogen, but of the absolute weight of each and the ratio between them.

If the diabetic patient were emaciated and contained little fat, fasting would be equivalent to throwing him upon an almost purely protein metabolism; and unless some toxic factor maintained too high a rate of protein metabolism in spite of the fasting, we would not expect a fasting acidosis. For protein alone does not cause acidosis if the glucose derived from it is oxidized and when the rate of protein metabolism sinks low enough, even the severest cases of diabetes can oxidize all the glucose that is formed from protein. This follows from what was said at the beginning of the paper. In a case recently studied by Geyelin and Du Bois fasting caused a marked diminution of the acidosis even while the protein metabolism was relatively high and the G : N ratio in the urine was still 3.65 to 1. The fasting in this instance doubtless served to

cut down the great preponderance of fatty acids in the metabolic mixture.

I have not been able to share the view expressed by some that the lessening of diabetic acidosis during starvation is in any sense a paradox, nor to see the truth of statements to the effect that "fasting lowers acidosis in diabetes while in non-diabetics it causes acidosis." Our own experience is that diabetics have acidosis about as soon and in about the same degrees as non-diabetics *when there is reason to think they are metabolizing similar mixtures of foodstuffs during the fasting.* Fasting will lower acidosis either in health or in diabetes if it has the effect of stopping a one-sided metabolism and throwing the tissues on a balanced ration of fatty acids and glucose. To be sure diabetics far and wide are much more likely to have lost a considerable part of the body fat, and so in fasting are more prone to be thrown back upon an almost purely protein metabolism of low absolute magnitude which is not a ration productive of acidosis. But normal individuals in comparable states of nutrition behave in exactly the same manner. And if diabetics are very fat, it may happen that fasting results in no cessation; yes, even in an increase of acidosis—as with the non-diabetic obese. In this connection it may be recalled that every case of severe diabetes—if he receive any diet whatsoever—promptly eliminates most of that which is already carbohydrate or which can be converted into carbohydrate in the body, and so leaves his tissues on what is tantamount to a purely fat diet. Fasting in the case of severe diabetes, therefore, is in effect comparable to the discontinuance in health of a heavy diet consisting wholly of fat.

In perfectly normal individuals it is not possible, by the use of ordinary foods and methods of feeding, to cause excretions of acetone, beta-, keto- and betahydroxybutyric acids in such amounts as may occur in the severer forms of diabetes, even if the non-diabetics receive diets consisting wholly of fat. This is due primarily to the fact that in normal individuals even on such diets, the rate of oxidation of glucose derived from body protein and from glycerol is considerable and suffices for the complete oxidation of some of the fatty acid; and, secondarily, to the fact that there is a limit to the height to which the fat metabolism can be driven by fat feeding

a limit fixed by the limited rate at which fat can be absorbed from the bowel no matter how much may be fed. Wherefore, it is impossible by fat feeding in health to create so wide a divergency of the fatty acid from the glucose oxidation rate as that which can occur in diabetes. Nevertheless the fat-fed individual may develop a far greater surplus of fatty acids in the metabolic mixture while he is upon a wholly fat diet than the same individual will have during a fast, particularly if he happens to be a lean subject. And if the fat-fed case is fasted, *his* acidosis diminishes or wholly disappears. This phenomenon is the equivalent in non-diabetics of the seemingly anomalous phenomena of fasting in diabetes.

VARIATIONS

Occasionally we have encountered diabetic individuals in whom the acidosis has shown anomalous variations difficult to explain in terms of the proportions of glucose and fatty acids undergoing simultaneous oxidation in the body as a whole. How are these to be explained? Dr. Howland has spoken of acidosis occurring in infants without diabetes and in spite of balanced diets. Analogous phenomena may be seen in certain types of infection in adults, notably in the so-called "milk sickness" studied by Jordan and Harris, and in some streptococcus infections. In such cases there need be no disproportion of glucose in the diet, the acidosis may antedate the abstinence from food, and there is no evidence of a general disability on the part of the body as a whole to utilize glucose.

In this connection it is interesting to consider the question of *where* in the body acetone, beta-, keto- and betahydroxybutyric acids are chiefly formed and *where* under ordinary conditions glucose exerts its normal antiketogenic effect. There are ample experimental reasons for assuming that the greater proportion of all the acetone bodies formed in the body are created in the liver and muscle cells. The liver especially, if we may judge from perfusion experiments, seems to constitute the largest acetone factory and the principal site of the normal interaction between oxidizing fatty acids and oxidizing glucose. In such cases of acidosis we

might therefore think of infections or of inherited abnormalities, *or of both together*, affecting particularly the liver cells and so preventing locally that reaction between oxidizing glucose and fatty acids which normally inhibits any considerable accumulation of the acidosis compounds. How such an interference might be effected is a question which would involve a detailed discussion of the nature and mechanism of the phenomena known as "*antiketogenesis*," which time prohibits.

But whatever the mechanism in such cases may be, it can be assumed with safety that no individual, merely because of an accident to his pancreas of such a nature that he develops the symptoms which justify our calling him a case of diabetes, will by virtue of this accident become immune to infections or rid of metabolic abnormalities which he may have had before. On the contrary, there is accordingly reason to expect that occasionally an individual who happens to have a subnormal endocrine function of the pancreas may also have other anomalies or pick up an infection of the kind mentioned.

It would seem very pertinent in all discussions of acidosis in diabetes to make a clear distinction between true diabetogenous acidoses and non-diabetogenous acidoses occurring by accident in diabetic individuals. No little confusion is thus avoidable.

ACIDOSIS IN ACUTE AND CHRONIC DISEASE

By CHANNING FROTHINGHAM, Jr., M.D.
BOSTON, MASS.

The term acidosis as it is used in medicine at the present time does not designate a definite clinical entity, but is applied to a variety of conditions in which, as Sellards[1] expresses it, there is a general impoverishment of the body in bases or substances which readily give rise to bases. This impoverishment in bases may be due to faulty absorption of bases, to an unusual loss of them from the body, or to their neutralization by abnormal amounts of acids. Increase in the amounts of acids in the body may be due to the production of abnormal acids, an overproduction of the usual body acids, or, as Howland and Marriott[2] have recently suggested, to an accumulation of normal acids due to failure in excretion.

It is difficult, if not impossible, at the present time to estimate what are the normal amounts of bases and acids in the body. Probably considerable variation occurs under different physiological conditions. Y. Henderson recently emphasized the variations that occur in healthy subjects in some of the tests for so-called acidosis due to changes in elevation above sea level.

The methods used in testing for evidence of so-called acidosis are numerous. They consist in a direct examination of the blood, a study of the urine, a study of the products of respiration, and an estimation of the amount of alkali necessary to render the urine alkaline when administered by mouth or intravenously.

In the direct examination of the blood for evidence of so-called acidosis many studies have been made of the carbon dioxide content of the blood. It has been known for a long time that this acid dim-

inishes in amount in the blood as other acids increase, except when variations in the excitability of the respiratory centre occur, as Hasselbalch[3] and others have pointed out. A diminution of the carbon dioxide in the blood, therefore, has been looked upon as evidence of acidosis. Pflüger,[4] Senator,[5] Geppert,[6] and Minkowski[7] were conspicuous among the early workers on the subject of diminished carbon dioxide in the blood in fevers. Their work, which was carried out on animals under different experimental conditions, consisted in direct examination of either the venous or the arterial blood. The lowering of the carbon dioxide content in the blood which they found in fevers was considered to be due to an increase in other acid substances. In 1889 Kraus,[8] applying this test to man, found that the amount of carbon dioxide in the blood was diminished in fevers. He studied a few cases of typhoid fever, tuberculosis, erysipelas, scarlatina, pneumonia, and acute articular rheumatism. In 1912 Peabody[9] studied the carbon dioxide content of the blood in pneumonia and found it usually low, occasionally normal, and rarely above normal. In the severer cases and terminal stages of the disease the carbon dioxide was usually low. Van Slyke[10] has recently devised a relatively simple method of estimating the amount of carbon dioxide in the blood. This method should be of great assistance in detecting acidosis.

Studies upon the hydrogen ion concentration of the blood for evidence of acidosis have been made by Peabody[11] in chronic nephritis and cardiac cases. He found the hydrogen ion concentration of the blood remained quite constant in his cases. Rolly[12] has made an extensive study of the hydrogen and hydroxyl ions in the blood in a variety of diseases and concludes from his observations that the alkalinity of the blood is lowered in diabetes, nephritis, severe anemia, and the gastro-intestinal diseases of childhood, while on the other hand, in diseases of the liver and in Graves's disease the alkalinity of the blood is increased.

In 1888 v. Jaksch[13] reported a diminished alkalinity of the blood in uremia, fever, destructive liver disease, leukemia, chlorosis, primary anemia and carbon monoxide gas poisoning. In 1914 Sellards[1] estimated the titratable alkalinity of the blood in various conditions in which acidosis is present, as shown by other tests, and found it

diminished. He also found it lowered in certain chronic nephropathies and in some anemias.

In 1913 Marriott[14] reported a method for estimating the amount of oxybutyric acid in a small amount of blood collected from a vein, and in 1914[15] showed that although traces of this acid might be present in the blood during health, it was increased ten- to twentyfold in the acidosis of diabetes. Recently, Howland and Marriott[16] have reported that different acid substances, especially the acid phosphates, are increased in amount in the blood of patients with chronic nephritis.

It is to be expected that further studies on human blood will reveal cases in which normal acids are increased in amount in the blood in different diseases, or in which acids are present which are not present under normal conditions.

In considering the methods advocated for detecting the presence of acidosis by examination of the urine no attempt will be made to completely review the subject. Attention will simply be called to certain of the tests which have been used considerably of late by investigators. It must be remembered that just criticism has been raised against most of these urinary tests for acidosis because they simply show what is excreted, and not what remains in the body. Careful studies have shown that frequently the body is unable to excrete in the urine those substances which have been looked upon as indicative of acidosis.

Since Stadelmann[17] discovered oxybutyric acid in the urine of diabetics in 1883, the presence of this substance or diacetic acid or acetone in the urine have been looked upon as an indication of acidosis. At one time the amounts of these substances in the urine were used as indications of the degree of acidosis, but it has now been shown definitely that considerable amounts of oxybutyric acid may be present in the blood with only traces of acetone in the urine. On the other hand, there seems to be always some trace of acetone in the urine when there is much oxybutyric acid in the blood. Von Noorden[18] mentions in his book that acetone has been found in scarlatina, measles, typhoid, and severe dysentery. Howland and Marriott[2] consider that it occurs in most of the infectious diseases of childhood just as fever does. In addition to the

above Taylor[19] found acetone in the urine in eclampsia and phosphorus poisoning. It is also well known that acetone bodies occur in the urine in starvation and after anesthesia. Therefore acetone in the urine may be looked upon as an indication that abnormal acids are present in the blood, but it is no indication of how large a quantity of them are present.

The relation of the amount of ammonia to the total nitrogen in the urine has been studied as an indication of excessive production of acid substances in the body. An increase in the relative amount of ammonia is looked upon as an indication of so-called acidosis, although it must be borne in mind that certain diets rich in proteid and diseases which cause a large breaking down of proteid may show a relative as well as actual increase in ammonia nitrogen in the urine. Boussingault's[20] observation in 1850, that the ammonia in diabetic urines was increased, was brought to the attention of medical men again in 1880 by Hallervorden.[21] Since that time many observers have confirmed this fact and used it as a means of determining the degree of acidosis, especially in diabetes. Sellards[22] has found the ammonia in the urine increased in Asiatic cholera. Pfaundler[23] reports it increased in diseases of the liver and in gastro-intestinal disorders of children. Palmer and Henderson[24] feel that the increase in ammonia in the urine indicates the degree of acidosis only in those cases in which the acidosis is due to the formation of oxybutyric acid. Howland and Marriott[2] perhaps sum up the question of the relation between a relative increase in the ammonia in the urine and acidosis by saying that such an increase suggests an acidosis but needs confirmation by other tests.

In recent years studies have been made upon the hydrogen ion concentration of the urine as estimated by Henderson's method. Henderson and Palmer[25] found that in certain diseases the average hydrogen ion concentration was lower than in healthy persons, but the individual variations in the different groups makes the test unreliable.

Since Haldane and Priestley,[26] in 1905, devised a relatively simple method for determining the amount of carbon dioxide in the alveolar air, this test has been much used for studies on acidosis; for it is well known that the alveolar carbon dioxide corresponds closely to

that in the arterial blood, and as other acids increase, this acid diminishes in amount in the blood. Thus a reduction of the tension of the carbon dioxide in the alveoli is looked upon as an indication of acidosis unless changes in the irritability of the respiratory centre are present.

V. Rubow[27] and Beddard and Pembrey,[28] in 1908, found a lowered carbon dioxide tension in the alveolar air in cardiac cases which showed cyanosis. Fitzgerald[29] also found the carbon dioxide tension in the alveolar air below normal in cases of congenital heart disease. Beddard and Pembrey[28] found evidence of acidosis by this test in diabetes. Porges,[30] Leimdorfer and Markovici confirmed this finding and found also that the carbon dioxide tension was lowered in cardiac dyspnea. Friderica and Olsen[31] report evidence of acidosis as shown by this test in some cases of erysipelas, mumps and angina, but not uniformly. Straub and Schlayer,[32] in 1912, found the carbon dioxide tension diminished in the alveolar air in cases of chronic nephritis. Evidence of acidosis in certain cases of chronic nephritis as shown by this test has also been found by Peabody,[33] Porges and Leimdörfer[34] and others. Roth[35] reports evidence of diminished carbon dioxide tension in the alveolar air of cases of obesity and in certain surgical cases.

The estimation of the degree of acidosis by determining the amount of bicarbonate of soda taken by mouth or intravenously, which is necessary to render the urine alkaline, has been used extensively by Sellards. He[36] found increased tolerance to soda bicarbonate in some of the nephropathies, Asiatic cholera, some anemias, rheumatic fever, and diabetes. Henderson and Palmer,[24] in 1913, applied the principle of this test in a somewhat different form and found evidence of acidosis in nephritis. Peabody[37] has also found evidence of acidosis by the so-called soda tolerance test of Sellards in nephritis.

It is evident from this short review that signs of so-called acidosis as detected by various tests may exist in numerous diseases. In each disease, however, all the tests may not be positive, as, for example, acetone may be found in diabetes and in diseases in children, while in chronic nephritis it is not present; yet all of these conditions may show the alveolar carbon dioxide lowered or the soda tolerance

increased. It would seem, therefore, that so-called acidosis is not due in each case to the same abnormal factors.

It has been the object of this work to study on the same case at the same time several of these tests for so-called acidosis with a view to finding out how the cases, in which an acidosis is supposed to exist, react to the different tests. Also it was thought that evidence of acidosis might appear in certain diseases in which its presence has not as yet been expected.

For this purpose cases were selected from the wards of the Peter Bent Brigham Hospital for study. So far as possible cases were chosen which presented an uncomplicated picture of a single disease. In each case the carbon dioxide tension in the alveolar air was determined, the soda tolerance test was carried out, and the twenty-four-hour specimen of urine was examined for the presence of acetone, for its hydrogen ion concentration, for the total nitrogen, and for the ammonia nitrogen.

The Plesch[38] method as modified by Higgins[39] was used for collecting the alveolar air which was then examined by the method devised by Haldane[40] for gas analysis. That this method is satisfactory even in cases in which the patient is breathing rapidly or is unable to coöperate with, the investigator has been shown by Walker and Frothingham.[41] We (Walker and Frothingham) compared the results obtained by this method with the results obtained by examination of the venous blood direct, as recommended by Van Slyke, and found that they agreed very well in most cases. With this method under these conditions it seems fair to call the carbon dioxide tension normal when it falls between 39 and 45 mm. The alveolar air in each case was collected for examination at some time during the twenty-four hours in which the urine was collected or just after the twenty-four hours were up on the following morning before the soda tolerance test was started. Most of the samples of alveolar air were collected about two or three hours after a meal.

In studying the amount of bicarbonate of soda necessary to make the urine alkaline to litmus, 5 grams at a time were given by mouth. At the end of two hours the patient voided the urine and if it was still acid the dose was repeated. If the patient was unable to void, the next dose was put off until after the next urination. If the test

was carried on through the night, patients were not aroused, so the intervals became longer. It usually takes from 5 to 15 grams of sodium bicarbonate to change the reaction of a healthy person's urine from acid to alkaline. In a few cases the urine became amphoteric, in which cases the test was continued until it became definitely alkaline to litmus. This test was performed in the morning after the twenty-four-hour urine had been collected.

In the twenty-four-hour urines a small amount of toluol was used as a preservative. In some cases due to contamination with feces or to errors on the part of those collecting the urines the full twenty-four-hour amount was not obtained, but it was felt that probably these losses made little difference in the relation of ammonia to the total nitrogen.

The ammonia is recorded as ammonia nitrogen. This and the total nitrogen of the urine were estimated by Folin's[42] method. The ammonia nitrogen is usually estimated at about 2 to 7 per cent. of the total nitrogen under normal conditions.

The hydrogen ion concentration of the urine was determined by Henderson's method and recorded as the logarithm with the minus sign omitted. Henderson and Palmer[25] found the average of 100 healthy cases to be Ph. 6.3. The presence of acetone was looked for by shaking the urine with glacial acetic acid and sodium nitroprusside and then adding ammonia. No attempt was made to quantitate this substance.

TABLE I.—SYPHILIS

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2-N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate, grams.
Nov. 5, 1915	3540	42.0	2.9	7.3	0	5
Jan. 6, 1916	3857	44.2	2.8	5.9	0	10
Feb. 17, 1916	4143	43.2	5.5	5.8	0	5

The results of these studies are presented in the form of tables. Cases of the same disease are grouped together in one table and a few words of explanation are added to emphasize the interesting points. The actual date of the observation and the medical number of the patient are recorded so that by reference to the hospital records the exact condition of the patient at the time of the tests may be ascertained.

In Table I are grouped three cases of syphilis which showed evidence of a generalized infection with the spirochetes. It will be readily seen that in each case all the tests fall within normal limits, and therefore no suggestion of acidosis is present.

In Table II are included two cases of epilepsy on whom the tests were taken between attacks which came only in infrequent intervals. In these cases there is no evidence of acidosis in any of the tests used.

TABLE II.—EPILEPSY

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH N_2–N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate, grams.
Nov. 3, 1915	3517	42.7	5.0	5.6	0	10
3, 1915	3514	39.1	6.3	5.8	0	10

Six cases of diabetes are presented in Table III. In 5 of these cases it will be seen that there is evidence of acidosis, and furthermore, that each of these 5 cases show variations from the normal in all of the tests used except in the hydrogen ion concentration of the urine. As will be observed in the other groups, this test shows such marked variation in the individual cases that it does not seem to be reliable as a guide to acidosis. The remaining case was a mild case and

TABLE III.—DIABETES

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2–N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate, grams.
Dec. 14, 1915	3738	34.7	18.2	6.2	+	35
15, 1915	3746	36.6	11.2	5.1	+	45
15, 1915	3757	34.6	18.9	Below 4.7	+	65
Jan. 4, 1916	3880	32.3	20.4	5.9	+	60 amphoteric. 90 total.
24, 1916	4008	40.8	4.6	5.0	0	10
25, 1916	3988	35.5	10.3	5.5	+	55

showed no evidence of acidosis by any of the tests. If we assume that the acidosis of diabetes is due entirely to the presence of increased amounts of oxybutyric acid, we may expect that acidosis due to this cause in other diseases will give positive results with all these tests except the hydrogen ion concentration of the urine. Of course other factors than oxybutyric acid may take part in the acidosis of diabetes.

Quite a different condition from the acidosis in diabetes is seen in the 9 cases of Graves's disease in Table IV. These cases represent various degrees of activity of the disease. In some of these cases the CO_2 tension in the alveolar air was quite high. Acetone was never present, and the urine became alkaline on small amounts of

Table IV.—Graves's Disease

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2–N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate, grams.
Nov. 4, 1915	3434	54.4	2.8	7.3	0	15
16, 1915	3591	47.2	2.8	6.3	0	10 amphoteric. 15 total.
Dec. 16, 1915	3792	43.5	6.9	6.4	0	10
16, 1915	3748	45.4	7.0	5.8	0	10
Jan. 13, 1916	3896	47.7	2.1	4.7	0	5
21, 1916	3989	41.2	7.6	5.9	0	5
27, 1916	4040	40.9	4.0	7.0	0	5
Feb. 1, 1916	4075	40.6	6.4	6.2	0	5
Mar. 17, 1916	4311	43.9	7.3	Below 4.7	0	10 amphoteric. 15 total.

soda in 4 of the cases. The percentage of ammonia nitrogen to total nitrogen varied considerably, but in no case did it reach 10 per cent. The hydrogen ion concentration shows variations from one end of the scale used to the other.

Table V.—Primary Anemia

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2–N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate, grams.
Oct. 23, 1915	3139	40.2	6.9	5.2	0	20
26, 1915	3435	41.2	4.0	6.6	0	10
Nov. 9, 1915	3538	39.7	5.8	5.2	0	10
29, 1915	3690	39.3	5.5	5.6	0	15 amphoteric. 20 total.
Jan. 12, 1916	3863	36.7	7.5	5.6	0	35 taking 1 c.c. dilute HCl t. i. d.
Feb. 4, 1916	4063	42.5	6.9	6.3	0	15
29, 1916	4064	38.6	4.0	5.2	0	20 taking 1 c.c. dilute HCl t. i. d.
29, 1916	4223	46.2	5.3	5.4	0	10

Eight cases of primary anemia with quite marked blood changes are shown in Table V. Evidence of acidosis is suggested in the alveolar air and soda tolerance tests in 2 cases but both of these cases

were receiving 1 c.c. of dilute HCl three times a day. In other cases the amount of soda necessary to render the urine alkaline was slightly elevated. The study of the ammonia-nitrogen ratio and the hydrogen ion concentration showed nothing remarkable. Certainly no appreciable degree of acidosis exists in this condition which is detectable by these tests.

Four of the 6 cases of advanced chronic nephritis in Table VI show evidence of acidosis by the alveolar air test and the soda tolerance test. The percentage of ammonia is low in most of the cases, which agrees with observations of other workers. Whether this is due to faulty elimination or to the fact that ammonia is not used by the body to make up the deficiency in base met with in chronic nephritis is not clear. As there is no acetone in the urine, it is evident that this acidosis is due to some other factor than that which is present in diabetes. The hydrogen ion concentration is fairly constant in these cases and somewhat lowered. Several other cases not included in the table, because all five of the tests could not be completed, showed a very marked reduction in the alveolar air, CO_2 tension. In 1 case it was as low as 19 mm.

TABLE VI.—CHRONIC NEPHRITIS

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2–N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate, grams.
Nov. 5, 1915	3507	44.0	6.5	6.2	0	10
8, 1915	3520	38.7	1.0	4.8	0	25+
8, 1915	3369	40.1	3.3	5.1	0	50
22, 1915	3597	37.3	4.3	5.1	0	10
Jan. 21, 1916	3990	39.5	4.2	5.8	0	25
Mar. 4, 1916	4253	29.9	2.8	5.5	0	40+

Twenty-one observations on 15 cases of pneumonia are recorded in Table VII. In those cases in which two observations were made the second one was after the crisis. Several of these pneumonias terminated fatally. Although the respirations in many of these cases were elevated, the results of the CO_2 tension determinations in the alveolar air checked up well with the estimation of carbon dioxide in the venous blood. Some of these cases during the course of the disease showed evidence of acidosis by this alveolar air test while others showed just the reverse. This fits in with Peabody's observation on the blood in pneumonia. He found the CO_2 low in

some, normal in some, and elevated in a few. In a few of the cases the ammonia fraction of the total nitrogen in the urine was elevated appreciably above normal. The hydrogen ion concentration of the urine was quite variable but on the whole tended to be toward the acid end of the scale. In 1 case acetone was present. In most of the cases during the height of the fever the amount of soda bicarbonate necessary to render the urine alkaline was considerably increased. In the cases in which a plus sign is put after the number of grams it signifies that the soda was discontinued for some reason before the urine became alkaline. This test certainly suggests that an acidosis is present during the course of the fever in some of these cases. An interesting feature in this group is the fact that the different tests for acidosis show more variable results than in other diseases with acidosis. It suggests, therefore, that if an acidosis is present in pneumonia, it may be due to some other factors than those that produce the acidosis in diabetes or chronic nephritis.

TABLE VII.—PNEUMONIA

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2-N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate, grams.
Nov. 13, 1915	3608	37.9	26.5	5.5	+	10
18, 1915	3630	40.3	5.8	5.4	0	55
19, 1915	3642	34.5	12.3	5.7	0	35+ discontinued.
23, 1915	3608	39.7	8.3	6.2	0	5 convalescent.
23, 1915	3630	33.8	2.5	6.4	0	10 crisis passed; beginning empyema.
26, 1915	3677	44.2	7.6	5.1	0	40
29, 1915	3699	45.9	9.8	5.3	0	15
Dec. 7, 1915	3699	47.6	7.7	6.1	0	15 convalescent.
8, 1915	3744	40.6	8.1	5.2	0	35+ discontinued.
31, 1915	3883	34.2	7.1	..	0	110
31, 1915	3882	34.7	5.0	..	0	30
Jan. 4, 1916	3885	42.0	5.6	5.4	0	25
10, 1916	3883	44.7	3.3	5.6	0	15 convalescent.
10, 1916	3882	41.9	2.9	6.0	0	5 convalescent.
14, 1916	3944	38.1	10.7	6.2	0	20 amphoteric. 35 total.
19, 1916	3965	41.6	5.6	5.2	0	20 broncho-pneumonia
27, 1916	4046	45.1	7.5	5.1	0	25
Feb. 5, 1916	4046	45.1	6.0	5.4	0	15 convalescent.
Mar. 7, 1916	4263	36.3	11.8	5.2	0	5 crisis on day before tolerance test was done.
7, 1916	4280	43.1	3.3	4.9	0	15
17, 1916	4237	38.8	9.7	4.7	0	20

In Table VIII are ten observations made on 8 cases of acute articular rheumatism. These cases were taking salicylate of soda at the time of the observations. In several of the cases evidence of acidosis was shown by the alveolar air studies but not in all of them. In 1 case acetone was present and in another the ammonia was elevated to nearly 10 per cent., but in the other cases these tests showed no evidence of acidosis. Four of the cases showed an increase in the soda tolerance test. The hydrogen ion concentration of the urine showed too marked variation to be of value in forming an opinion in this disease. It seems fair to say that some form of acidosis occurs in certain of these cases of acute rheumatism which shows up in one or the other of these tests but not consistently in any one.

TABLE VIII.—ACUTE ARTICULAR RHEUMATISM

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2–N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate, grams.
Dec. 2, 1915	3715	33.2	5.1	5.7	0	10
2, 1915	3712	37.1	6.5	5.4	+	15
3, 1915	3662	35.0	5.1	7.1	0	20
7, 1915	3715	41.0	2.6	4.9	0	10 convalescent.
8, 1915	3662	31.2	4.2	5.1	0	10
Feb. 3, 1916	4088	33.2	6.4	5.3	0	20
Mar. 23, 1916	4371	38.2	7.6	Below 4.7	0	40
27, 1916	4396	33.1	5.8	7.2	0	10
29, 1916	4417	44.5	6.4	5.6	0	20
Apr. 21, 1916	4534	43.3	9.8	4.9	0	15

Three cases of subacute nephritis of a mild grade are presented in Table IX and show no evidence of acidosis by any of the tests. In 2 the CO_2 tension in the alveolar air was rather high.

TABLE IX.—SUBACUTE NEPHRITIS

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2–N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate, grams.
Mar. 2, 1916	4160	39.5	7.1	6.0	0	10
22, 1916	4245	46.2	3.6	4.9	0	15
22, 1916	4314	48.5	2.9	5.2	0	10

TABLE X.—LUNG ABSCESS

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2–N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate grams.
Jan. 12, 1915	3834	40.4	3.2	5.6	0	15
Mar. 7, 1916	4226	41.2	8.2	5.2	0	10

Two cases of lung abscess shown in Table X also show no evidence of acidosis.

In 2 cases of gastric cancer (Table XI) the amount of soda necessary to render the urine alkaline was increased above normal in both. This may possibly have been due to some disturbance in absorption rather than an acidosis. Of the other tests the alveolar air suggested acdiosis in 1 case. The ammonia was high in this case also. The hydrogen ion concentration in the urine represented the two extremes of the scale.

Table XI.—Gastric Cancer

Date.	Med. No.	Alveolar air, Co_2 tension, mm.	NH_3N_2–N_2 per cent.	24-hour urine. Ph.	Ace-tone.	Soda bicarbonate, grams.
Mar. 20, 1916	4336	39.2	7.2	Below 4.7	0	30 amphoteric. 45 total.
23, 1916	3799	37.4	12.8	7.1	0	5 amphoteric. 35 total.

In 2 cases of Addison's disease (Table XII) the CO_2 tension was just below the lower limit of normal. In 1 case the soda tolerance test showed an increase. It is interesting to note that in both the cases the hydrogen ion concentration was more acid than a Ph. of 4.7, but conclusions from these 2 cases are hardly justifiable.

Table XII.—Addison's Disease

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2–N_2 per cent.	24-hour urine. Ph.	Ace-tone.	Soda bicarbonate, grams.
Oct. 29, 1915	3521	38.3	8.3	Below 4.7	0	35
Mar. 11, 1916	4299	38.7	2.4	Below 4.7	0	15

In 1 of the cases of cirrhosis of the liver (Table XIII) the ammonia was elevated, as has been noted in diseases of the liver. In the case which had ascites the soda tolerance test was increased. This has been the finding in other of our cases of ascites from portal obstruction and probably has some relation to the portal obstruction rather than to any acidosis.

In Table XIV are grouped 6 cases of chronic cardiac disease. In these cases compensation was fairly well established as long as the

patients were quiet in bed. Most of them preferred to have the head somewhat elevated. Except for a diminished carbon dioxide tension in 1 case and a slightly increased percentage of ammonia in another there is no evidence of acidosis. In both these cases the other signs of an acidosis were absent. The hydrogen ion concentration of the urine showed such marked variation that no conclusions could be drawn from it.

TABLE XIII.—CIRRHOSIS OF THE LIVER

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2–N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate, grams.
Feb. 2, 1916	4007	43.7	11.5	5.8	0	10
18, 1916	4170	38.2	6.0	5.1	0	25 (ascites).

TABLE XIV.—CHRONIC CARDIAC

Date.	Med. No.	Alveolar air, CO_2 tension, mm.	NH_3N_2–N_2 per cent.	24-hour urine. Ph.	Acetone.	Soda bicarbonate, grams.
Nov. 9, 1915	3523	34.8	3.7	6.4	0	5
10, 1915	3539	46.4	3.8	5.4	0	10
17, 1915	3632	39.1	4.8	7.4	0	5
Dec. 28, 1915	3730	43.2	6.4	4.7	0	10
30, 1915	3460	40.2	11.7	4.7	0	10
Jan. 31, 1916	4036	46.3	4.7	5.8	0	5

In Table XV are grouped 17 cases representing as many different conditions. In several of them interesting responses to the different tests are seen. In some of them quite marked evidence of acidosis occurs. Acetone was not found in any of these cases, so the type of acidosis was probably different from that found in diabetes. In the case with an acute infection involving the kidney, in the case of probable miliary tuberculosis and in the case of typhoid fever, evidence of acidosis was shown by the alveolar air study and the soda tolerance test. In 2 of these cases the hydrogen ion concentration of the urine showed it to be strongly acid. One case of gout was interesting in that it showed no evidence of acidosis. The case of portal thrombosis was of interest in that it showed a high percentage of ammonia nitrogen in the urine as is reported in liver disorders, and a high soda tolerance, which is probably due to the portal obstruction rather than an acidosis. The cases of lymphatic leukemia, portal

thrombosis and myxedema show a very slight reduction in the carbon dioxide tension of the alveolar air but too slight to make one feel that any appreciable acidosis exists. The case which suggested typhus was interesting in that the soda tolerance was increased, suggesting an acidosis, while the carbon dioxide tension in the alveolar air was high, suggesting just the reverse.

TABLE XV.—MISCELLANEOUS CASES

Date.	Med. No.	Alveolar air CO_2 tension, mm.	NH_3N_2 per cent.	24-hour N_2 urine. Ph.	Acetone.	Soda bicarbonate, grams.	Diagnosis.
Oct. 27, 1915	3522	36.4	7.9	6.1	0	20	Typhoid fever.
29, 1915	3423	41.6	3.1	5.6	0	15	Chronic arthritis.
29, 1915	3457	28.7	2.6	Below 4.7	0	30	Probably miliary tuberculosis.
Nov. 3, 1915	3559	42.2	4.6	5.6	0	20	Tumor in right kidney region.
10, 1915	3480	42.5	9.8	5.8	0	15	Fever—mild, unknown cause.
12, 1915	3566	41.7	7.8	7.2	0	10	Acute endocarditis.
Dec. 14, 1915	3787	41.9	5.2	5.0	0	10	Acute bronchitis.
21, 1915	3780	27.4	7.6	Below 4.7	0	80+	Acute infection involving kidney.
Jan. 6, 1916	3905	39.9	7.1	5.3	0	15	Gonorrheal arthritis.
12, 1916	3955	41.9	6.1	5.6	0	15	Perirenal abscess.
24, 1916	4025	45.9	7.5	5.4	0	30	Typhus.
25, 1916	4035	43.5	3.4	6.6	0	10	Erythema nodosum.
Feb. 1, 1916	3281	38.5	27.8	5.8	0	65	Portal thrombosis.
16, 1916	4166	45.9	5.4	5.2	0	15	Gout and alcohol.
21, 1916	4180	38.3	5.6	4.7	0	10	Lymphatic leukemia
28, 1916	4197	38.3	5.6	6.0	0	15 amphoteric 20 total	Myxedema.
Mar. 24, 1916	4359	46.7	6.4	6.4	0	10	Polycythemia.

From these studies it seems fair to conclude that the study of the hydrogen ion concentration in the urine is not reliable as an index of acidosis, and therefore it will not be considered further in this summary. It is also clear from this study that evidence of acidosis appears at times in certain diseases while in other diseases no evidence of it is found. Those diseases which showed an acidosis at times by some of these tests are diabetes, chronic nephritis, pneumonia, acute articular rheumatism and several acute febrile conditions in the miscellaneous group. Cases of Graves's disease, epilepsy, syphilis, chronic cardiac disease, subacute nephritis, lung abscess, and many in the miscellaneous group distinctly did not show any evidence of acidosis by these tests. The results in the cases of

primary anemia, gastric cancer, Addison's disease, and cirrhosis of the liver were not so clearly defined and in some of the tests suggested a slight acidosis.

It is evident from these tests that the acidosis found in diabetes is due to different causes, in part at least, from those that produce it in other conditions. It also seems likely that the acidosis met with in different diseases is due to various causes, since the response to these tests varies somewhat in the different conditions.

Of these tests either the estimation of the carbon dioxide tension in the alveolar air or the so-called soda tolerance test showed some variation from the normal in all the cases of acidosis. They also seem to be of value in detecting the degree of acidosis.

I wish to thank most heartily Miss Barker, Miss Russell, and Miss Cate, who as laboratory assistants helped me in carrying out the various estimations on the air and urines.

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THE DIAGNOSIS AND TREATMENT OF ACIDOSIS

By L. G. ROWNTREE, M.D., Sc.D.
MINNEAPOLIS

Theoretically and practically acidosis is of extreme interest: to the scientist, on account of the ingenious protective mechanism provided by nature for the maintenance of a constant acid base equilibrium; to the clinician, because of its frequency in many clinical conditions. Recently, new methods have been evolved which make possible early and more precise diagnosis, and furnish an insight into the mechanism whereby the acidosis develops. More ready clinical recognition of any condition leads to earlier and usually to more successful treatment, while information relative to the mode of production leads to successful prophylaxis and to rational therapy. These are desiderata of the greatest importance owing to the grave prognostic significance attaching to the development of severe acidosis, the suddenness of its appearance at times, and, above all, to the fact that proper therapy in some instances may tide a patient over a critical period.

The problems of acidosis are embraced in the larger problem of the maintenance of a constant acid base equilibrium in the body. The factors here concerned must be borne in mind since different mechanisms are unquestionably playing a role in the development of the various types of acidosis. That different types do exist is early evident to the student of the subject.

Though much has been written, little of fundamental importance has been added to our knowledge of the maintenance of this equilibrium since the masterly presentation of the subject by L. J. Henderson, in 1909.[1] Clinically, great strides have been made in

our knowledge of acidosis from the stand-points of methods and diagnosis and in our knowledge of its clinical associations.

One fact must be borne in mind. Idiopathic or primary acidosis is unknown. Acidosis is always secondary. It arises in the course of many pathological processes which in turn are influenced by its presence. It becomes a part of different vicious cycles. Its investigation is rendered more difficult by its manifold clinical associations. Variations in types which can be observed clinically or elicited through laboratory studies may frequently be dependent upon associated diseases.

Factors Maintaining Acid-base Equilibrium. Four great factors at least are concerned in maintaining acid-base equilibrium. These are (1) the excretion of CO_2 by the lungs; (2) the activity of the kidney whereby an acid urine is separated from blood which is alkaline; (3) the peculiar property of the blood—the so-called buffer action to acid and alkali; (4) finally, the formation of ammonia which aids in the neutralization of acid when the fixed bases are no longer available. Changes in regard to factors (1), (2), and (3) are almost invariably encountered when large quantities of acids are produced within the body or introduced from without. Increased ammonia production, however, is not a constant accompaniment of clinical or experimental acidosis. Certain features of each factor are worthy of special consideration.

1. *Respiration.* CO_2 is constantly transferred from seats of high to seats of low tension, *i. e.*, from the tissues, where the CO_2 is formed and where the tension is high, to the blood, to the alveolar air, and finally to the external air where its tension is lowest. In this process the $NaHCO_3$ of the plasma plays an extremely important role since stronger acids replace CO_2, which in turn is readily excreted, leaving a neutral salt. Henderson refers to the bicarbonate as the first line of defences. They protect the body from acids in the following way: $NaHCO_3 + HCl = NaCl + H_2O + CO_2$.

The equivalent of several hundred cubic centimeters of a normal acid is eliminated by the lungs in twenty-four hours.

2. *Excretion of Acid in Urine.* The kidneys excrete an acid urine while the blood supplying them is alkaline. In this way the body is freed of acid and acid phosphates while bases are saved to

the organism. Some alkali is excreted with the phosphate, but a new function of the kidney is now recognized, *i. e.*, conservation of bases.

Thus: $Na_2HPO_4 + HCl = NaCl + NaH_2PO_4$, the disodium phosphate serving to take care of both the acids. On the other hand the following reaction may occur, under which conditions the alkali or bicarbonate reserve of the blood is increased while acid is being excreted, $Na_2HPO_4 + H_2O + CO_2 = NaH_2PO_4 + NaHCO_3$. That this function of the kidney is one of great importance is shown by the fact that the alkali so saved approximates 200 to 800 c.c. $\frac{N}{10}$ NaOH per diem.

3. *The Buffer Action of Blood.* By the "buffer action" of a mixture is meant its ability to take up considerable amounts of acid or alkali when these are added to it without appreciable changes in hydrogen ion concentration. The blood is such a buffer mixture, owing largely to its content of carbonates, phosphates and, to a lesser extent, its protein.

Last year, in presenting the dialysis-indicator method before the Association of American Physicians, it was stated that it was being employed in a study of the buffer value of the blood. A report by Van Slyke, Stillman, and Cullen appeared in April, 1915, demonstrating the decrease in reserve alkalinity in acidosis. Our paper[2] appeared in the *Archives of Internal Medicine* for April, 1916.

Mode of Expression of Results. All results are expressed in terms of c.c. of $\frac{N}{50}$ HCl or NaOH per 2 c.c. of blood.

The final results appear in Table I, from which it is evident that the alkaline reserve of the blood is decreased, and in addition, what has not been recognized clinically, that the acid reserve or buffer against alkali is also decreased.* The total buffer value is therefore diminished.

4. Utilization of NH_3 after the fixed alkalies have failed occurs in acidosis associated with marked ketonuria. As already indicated, this mechanism, however, is not called into play at all in certain types of acidosis.

* The decrease is not constant since some instances of normal buffer in both clinical and experimental acidosis have been encountered in our study.

Table I.—Summary of Acid, Alkali, and Total Buffer Values for the Various Case Groups Expressed as Group Averages

		No. of cases and determinations.	Acid.	Alkali.	Total.
Normal individuals . .		24	0.18	0.18	0.36
9	True . . .	9	0.075	0.056	0.13
Acidosis		16			
24	Compensated	6	0.1	0.1	0.2
		8			

Laboratory Studies of Acidosis.* Value and Limitation of Methods. In this connection there are three general lines of approach: studies of the urine, the expired air, and the blood. These all reflect tissue changes. As nothing is known at present concerning tissue acidosis the pH of the blood is generally accepted as the index to acid base equilibrium of the organism as a whole. Unquestionably the blood studies constitute the most direct approach, although studies by indirect methods furnish extremely reliable and valuable data.

1. *Urinary Studies.* In the study of the urine the ammonia content, the quantity of acid bodies, the hydrogen ion concentration, and the reaction before and after the "alkali tolerance test"[3] are usually determined. In reality, information concerning renal function is also essential. In renal insufficiency the "alkali tolerance test" as now employed in the study of acidosis is not only useless, but is misleading. It is obviously impossible to base conclusions relative to the impoverishment of the tissues in alkalies on the failure of urine to become alkaline following the administration of cabonates or bicarbonates in amounts ordinarily sufficient to render it alkaline. The kidney simultaneously fails to excrete all other substances in normal fashion, with the possible exception of water. The findings cannot be interpreted, therefore, as indicating acidosis unless the excretory capacity of the kidney is known to be normal. This statement must not be interpreted as meaning that the test is not of value, but it does mean that the test is only applicable in selected cases.

* The writer wishes to acknowledge his indebtedness to Miss Winifred Swift for much technical assistance.

The ammonia of the urine may be increased or decreased, depending upon the type of acidosis. In diabetes and eclampsia, for example, it is of distinct importance, whereas in certain types of nephritis, as indicated by the studies of Palmer and Henderson, it has no great significance.

Acetone bodies (acetone, diacetic) appear in the urine under a large variety of conditions, but do not reflect the true state of the neutrality regulating mechanism. They are not constantly found in acidosis nor is their presence always indicative of its existence. Acidosis can exist without ketonuria. These terms are not synonymous, though often considered so.

The hydrogen ion concentration of the urine in health and disease has been carefully investigated by Palmer and Henderson.[4] The normal variations are so great that the findings have but slight clinical significance.

At best, studies of the urine yield information relating solely to the amount of acid excreted in the urine and not to the amount present in the blood and tissues. By inference they admit of certain deductions under definite considerations.

2. *Studies of Respiration.* The determination of the CO_2 of the alveolar air is an indirect but very valuable method of study in acidosis, the findings probably indicating approximately the bicarbonate reserve of the blood. Alveolar air may be collected by any one of several methods:* (*a*) Haldane,[5] (*b*) Plesch,[6] and (*c*) Fridericia.[7] The first and last necessitate intelligent coöperation on the part of the patient, whereas the Plesch method is generally applicable. Dr. R. L. Levy, who collaborated with me in Baltimore in these acidosis investigations, has perfected a mask which is fashioned somewhat after the one earlier employed by Dr. John King, of Baltimore. It utilizes the principle of rebreathing as described by Plesch. It has been used with the Haldane method in the CO_2 determinations here recorded.

Air collected by the Plesch-Levy method can also be determined in the Fridericia apparatus. The result of a series of such determinations is compared with those of the Haldane method in Table II.

* The details concerning this will appear in a separate publication.

TABLE II.—COMPARISON OF FRIDERICIA AND HALDANE METHODS OF DETERMINING ALVEOLAR CO_2 WITH PLESCH-LEVY COLLECTION

Case.	Hosp. No.	Temp.	Fridericia, mm. Hg.	Haldane, mm. Hg.	Remarks.
F. . . .	8477	22	29.8	29.6	Pregnancy at term.
C. . . .	8455	22	22.3	21.9	9 days postpartum.
P. . . .	8368	22	31.3	30.7	9 " "
L. . . .	8487	22	23.2	22.9	7 " "
S. . . .	8498	22	40.6	40.4	12 " "
B. . . .	8508	22	35.2	34.8	9 " "
H. . . .	8522	22	35.3	35.06	10 " "
C. . . .	. .	23	47.9	47.4	Normal.
Z. . . .	. .	23	44.3	44.0	Normal.
G. . . .	. .	23	49.2	48.9	Normal.

Peabody's[8] demonstration of increased sensitiveness of the respiratory center through rebreathing various percentages of CO_2 is an important addition to our knowledge of acidosis. But the effects of other factors, especially drugs (morphin) and various diseases upon the center, may modify or overshadow this influence.

3. *The Blood.* This is the logical and direct avenue of approach. Technical difficulties, however, lead to the introduction and use of the numerous indirect methods already described. Recent work has resulted in new methods which make the direct investigation possible clinically. The methods in use for studying the blood determine:

1. Hydrogen ion concentration.
   (*a*) Hydrogen electrode method.[9]
   (*b*) Dialysis-indicator method.[10]
2. The buffer value of blood—herein described.[11]
3. The alkaline reserve (Van Slyke).[12]
4. Titratable alkalinity (Sellards).[13]
5. The curve of hemoglobin dissociation (Barcroft).[14]
6. The quantity of acetone bodies (Schaffer and Marriott).[15]

The fact that the gas-chain method of determining the pH of the blood requires a delicate and expensive piece of physicochemical apparatus as well as considerable technical training has militated against its use in clinical medicine. Recently the dialysis-indicator method has been introduced. In collaboration with Dr. J. F. McClendon[16] I have had the opportunity of comparing its findings with those of the electrometric method (Fig. 1) as devised and used by him. Samples of blood from various sources have been taken, inde-

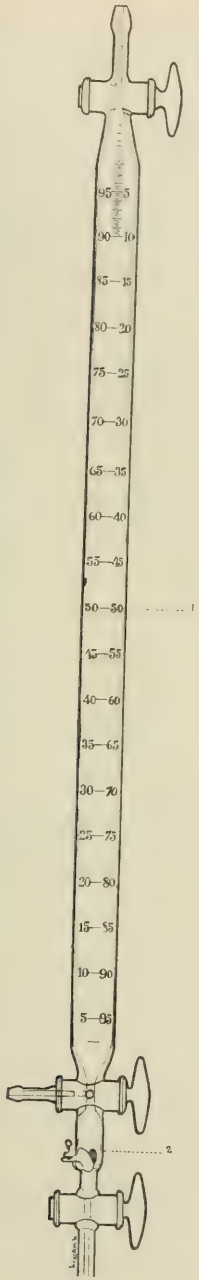


FIG. 1.—McClendon's combined tonometer and hydrogen electrode. 1. Mixing chamber. 2. Electrode. To appear shortly in Jour. of Biol. Chem.

pendent readings being made on them by the two methods. The results of this study appear in Table III.

TABLE III.—pH AS DETERMINED BY THE ELECTROMETRIC AND THE DIALYSIS-INDICATOR METHODS. DETERMINATIONS WITH ACCURATE CONTROL OF CO_2 TENSION*

No.	Material, 1.5 c.c.	CO_2 tension, per cent.	pH. Electrometric.	pH. Dialysis-indicator.
1	Plasma	1	8.05	8.1
2	"	3	7.9	7.9
3	"	5	7.6	7.6
4	"	10	7.43	7.4
5	"	10	7.4	7.4

EXPERIMENTAL DATA

Dog.	Weight, kg.	Condition.	pH. Electrometric.	pH. Dialysis-indicator.
Ia	11.1	Normal	7.5	7.5
b	..	150 c.c. $\frac{N}{2}$HCl	6.8	6.8
c	..	180 c.c. 8% $NaHCO_3$	7.5	7.5
d	..	465 c.c. 8% $NaHCO_3$	7.7†	7.65‡
II	11.8	In shock	7.2	7.15
IIIa	17.1	Normal	7.4	7.4
b	..	In shock	7.2	7.15

CLINICAL DATA

Patient.	Hospital No.	pH. Electrometric.	pH. Dialysis-indicator.
T.	8140	7.5	7.45
E.	8234	7.5	7.5
S.	8236	7.6	7.6

(See Fig. 1.)

More satisfactory agreement§ could not be desired. The rapidity and ease with which absolute values are obtained by the new method warrants its wide use in studies‖ of either acidosis or alkalosis.

* McClendon's combined tonometer and hydrogen electrode.

† Electrometric method on arterial blood.

‡ Dialysis-indicator method on venous blood.

§ More intimate acquaintance with the dialysis-indicator method demonstrates that great precautions are necessary in order to minimize the loss of CO_2. Blood is therefore drawn directly into a specially devised tube provided at each end with rubber connection and pinch cocks. Distally is attached, by the rubber connection, a second tube which is also partially filled before the clamps are applied. Blood is therefore drawn without exposure and without loss of CO_2. The desired amount of blood is allowed to flow into the dialyzing sac, which is lowered into the salt solution. The upper part of the sac is cut off and the tube stoppered during dialysis. Prolonged constricting by a tourniquet must be avoided in the collection of blood.

‖ Dialysis also offers an excellent opportunity for the study of abnormal acids present in the blood in acidosis. In the recent vividiffusion experiments of Abel, Rowntree and Turner,[17] lactic acid, β-oxybutyric acid, alanin, valin and histidin were isolated. A study of the dialysate from the blood in acidosis would unquestionably prove profitable.

Since a change in the pH only obtains after the protective mechanism has failed, peculiar significance attaches to its presence. Obviously compensated grades of acidosis will not be detected unless resort is had to one of the other tests.

The buffer value of blood has already been discussed. Scientifically these studies throw an interesting side light on the mechanism involved in the production of acidosis, but inasmuch as the total buffer value is not always decreased in acidosis and as the method as described requires considerable time and labor it will probably not come into wide use clinically.

The alkaline reserve or bicarbonate content of the blood as determined by Van Slyke yields information of the greatest significance clinically and scientifically. The method is readily applied, yields reliable and valuable data, and will unquestionably play a very important role in all future studies of the subject.

Sellard's test of titratable alkalinity yields valuable empirical data. It is to be commended for its simplicity. It is a gross index of acidosis and can be used by those lacking the time and equipment for the more refined methods.

With the curve of the *hemoglobin dissociation* my acquaintance has been too casual to justify an expression of opinion. Technical difficulties preclude its wide use in a clinical procedure.

The quantitative method of determining the acetone bodies in the blood is unquestionably of great importance, particularly in diabetes, but it is technically removed from general use.

Essentials in Determining Acidosis. The number of methods has increased to such an extent that it is essential to determine which can be discarded without loss and also what test or combination of tests yields all the desirable information in a given case. This necessitates an intimate familiarity with the applicability, limitations and significance of each test.

In my opinion the most essential factors to determine are the reserve alkalinity, the alveolar CO_2, and the pH of the blood. The best methods* are: for the first, the Van Slyke method; for the second, the Plesch-Levy collection, with gas analysis by the Haldane

* Marriott has recently introduced colorimetric methods for the determination of alveolar CO_2 and alkaline reserve which may prove to be extremely valuable.[15]

apparatus; and for the pH, the dialysis-indicator method. These yield quantitative data and indicate whether acidosis exists, whether it is compensated or absolute. Depending upon the underlying disease and the type of acidosis, other tests are desirable at times.

Acidosis and Nomenclature. If I desired to precipitate a discussion I would merely ask the question, What is acidosis? The term itself is a misnomer, since a pH greater* than 7.0 is rarely or never encountered clinically. Acidosis is a loosely used term. This Association would do a real service were it to appoint a committee to consider the question of nomenclature.

Inasmuch as this paper discusses acidosis, it becomes necessary to declare my attitude in this connection. Our custom has been to call all cases with a pH of the blood greater† than 7.4, *true acidosis;* all cases showing a normal pH but a decrease in alveolar tension and in the alkaline reserve of the blood, *compensated acidosis.* That this is far from ideal is admitted since "acidosis," though universally sanctioned, is a misnomer and since compensated acidosis is used to express an acidosis that is not an acidosis since a change in the pH of the blood has been prevented. Hasselbach[19] has also made this distinction.

Clinical Evidence of Acidosis. Clinical Associations. In acidosis respiratory changes are usually present. Hyperpnea (air hunger) is extremely common, but not absolutely constant. It always suggests acidosis and demands investigation. It does not invariably indicate acidosis for unmistakable hyperpnea has been encountered at times in animals, the subjects of experimental alkalosis, *i. e.*, in animals receiving large quantities of $NaHCO_3$ intravenously. The so-called acetone odor of the breath is most frequently encountered in cases showing ketonuria.

Acidosis is found in association with the following diseases and conditions:

1. Diabetes.
2. Renal, cardiorenal and cardiac disease.
3. Cachectic states and severe anemias.
4. Severe diarrhea (particularly in children).[20]

* By "Greater pH" is meant a greater "H" ion concentration, *e. g.*, pH 7.3 indicates a H ion concentration greater than pH 7.4.

† Ibid.

5. Cholera. Sellards.[21]

6. Starvation.

7. Pregnancy[22] and eclampsia.

8. Postoperative or postanesthetic conditions, particularly in surgical shock.

9. Certain febrile diseases.

During the course of the last two years, out of several hundred patients on whom some of these studies have been made, between 30 and 35 cases of true acidosis have been found. A few of the more interesting results will be considered.

Acidosis in Diabetes. 1. G. V. H., Med. No. 33876, Johns Hopkins, showed marked air hunger, urinary ammonia of 3 gm., and pH 7.25. After receiving 500 c.c. of 4 per cent. $NaHCO_3$ the pH was 7.45, this persisting for twenty hours. The acetone bodies, determined as acetone by Dr. Marriott, were 240 mgm. to 100 gm. of blood. The patient died in typical coma, the blood serum before death reading 7.65, *i. e.*, normal.

This indicates that death was not due to increased hydrogen ion concentration of the blood and is in keeping with the findings of Ehrmann and Esser[23] who demonstrated that the sodium salts of oxybutyric acid are capable of producing symptoms analogous to those found in diabetic coma.

The importance of this finding cannot be too strongly emphasized, since it indicates that alkali is of value in diabetic acidosis only in so far as it corrects the acidosis. I have seen at least three diabetics die after alkali therapy which resulted in the return of pH of the blood to normal. The condition of tissues, however, remains unknown. Alkali therapy should be used with a specific object in view and the amount should be controlled by laboratory studies. I have seen patients receive $NaHCO_3$ in amounts closely approximating in grams per kilogram the lethal dosage for dogs.

Acidosis in Renal and Cardiorenal and Cardiac Disease. At times acidosis plays a definite role in renal, cardiorenal and cardiac diseases. It may or may not develop in marked renal insufficiency. The findings in a fatal case of chronic interstitial nephritis (small granular kidney) seen in consultation with Dr. J. P. Schneider of Minneapolis emphasize the importance of such studies. The results appear in Table IV.

TABLE IV.—UREMIA AND ACIDOSIS. R.—SWEDISH HOSPITAL

Date.	Alveolar CO_2, mm. Hg.	pH, blood.	CO_2 cap. of plasma, c.c. of CO_2.	Urea N., mgm.	T. n-p. N. per 100 c.c.	Creatinine, bl.	Phthalein and Ambard's constant.	Remarks.
April 17	29.72	7.2	..	97.0	171	..	Ph. 7 per cent.	$NaHCO_3$ 15 gm. daily.
April 19	26.15	7.3	30.4	181.0	206	24	Ph. trace Am. con. 1.02	600 c.c. 4 per cent. $NaHCO_3$ I. V.
April 20	25.67	7.5	37.57	158.0	203	19	Am. con. 1.09	
Before April 22	..	..	24.59	91.0	171	..	..	600 c.c. 4 per cent.
After	..	7.6	26.45	..	..	..	..	$NaHCO_3$ I. V.
April 24	30.4	7.45	..	87.0	162	..	Am. con. 0.41	
Before April 25	..	7.3	31.7	84.5	..	..	..	Transfusion.
After	39.4	7.45	31.94	67.0				

In the acidosis accompanying renal insufficiency the CO_2 of the alveolar air may be tremendously decreased, in one instance reaching as low as 7 mm. Hg., and in 4 of our cases lower than 12 mm. Hg. The acetone bodies did not accumulate in the blood nor was there increase in the urinary ammonia in 2 of these cases in which these features were determined. Temporary benefit, in the clearing up of coma, in the relief of dyspnea, and in urinary secretion, together with increase in reserve alkalinity of the blood and correction of the pH, are observed at times following the administration of alkali. But I have yet to see anything approaching permanent results under these conditions except in one instance of renal insufficiency and acidosis accompanying an acute exacerbation in a case of chronic nephritis.

The role of acidosis in the production of dyspnea in patients with uncomplicated valvular disease and acute decompensation[24] is slight. The dyspnea exists with and without acidosis but the acidosis is more marked and appears only during the very acute stage, rapidly disappearing with clinical evidence of improvement. But in cardio-renal disease, as might be expected, it becomes a more important factor.

Acidosis in Cachexia and Anemia. In cachexia and anemia acidosis is occasionally encountered.

S., a case of carcinoma of the stomach, with marked metastases in the liver, died in profound coma with acidosis showing a pH of 7.35, a positive Sellard's test, an alveolar CO_2 of 11.4 Hg., and a decreased reserve alkalinity. Typical air hunger was present. In experimentally induced anemia in a dog acidosis did not develop after reducing the Hb. to 45 per cent. by repeated bleedings. (See Table V.)

Table V.—Effects of Bleeding

Dog.	Time.	Weight in kgm.	Alveolar CO_2 in mm. Hg.	Alkaline reserve in mm. Hg.
I.	June 14, 1916:			
	Before bleeding	17.0	39.83	29.13
	Immediately after bleeding 500 c.c.	. .	39.83	30.0
	June 16, 1916	16.3	38.83	46.51
II.	June 14, 1916:			
	Before bleeding	21.8	40.57	37.38
	Immedately after bleeding 600 c.c.		40.5	37.38
	June 16, 1916	21.5	41.03	44.67

Acidosis in Pregnancy and Eclampsia. It has been claimed that acidosis occurs in pregnancy.[25] True acidosis does not occur, and compensated acidosis, when present, is negligible.

The association of acidosis with eclampsia is interesting. Our series is too small to admit of any conclusions relative to its constancy; 8 cases only have been studied; true acidosis was present in 5. The findings appear in Table VI.

Table VI.—Acidosis in Eclampsia

Name.	Date.	pH.	Alveolar CO_2.	CO_2 of blood.	Remarks.
K.	. .	7.3	. .	. .	Recovery.
H.	June 9, 1915	7.3	. .	. .	T.n.P.N., 307 mgm.; urea N., 256 mgm.; alk. tolerance 15 gm.+.
B.	April 28, 1916	7.35	30.38	24.67	Died.
H.	April 29, 1916	7.35	23.02	25.3	Recover.
P.	May 2, 1916	7.45	. .	33.22	Puerperal convulsions.
S.	June 3, 1916	. .	35.0	34.9	Died.
L.	June 22, 1916	7.35	35.0	33.0	Convulsions.
H.	June 27, 1916	7.5	35.3	39.0	

Blood from the cord of the baby in Case II was secured and the pH of the serum determined as 7.3. Both patients recovered in spite of the acidosis.

These findings in eclampsia carry therapeutic significance, and indicate that alkali therapy should be tried.

Acidosis in Anesthesia and Surgical Shock. Four post-operative cases exhibiting clinical evidences of acidosis were studied: 2 prostatectomies, 1 nephrotomy, and 1 drainage of gall-bladder, with bile peritonitis. All showed true acidosis.

Clinically we have had no opportunity for the study of acidosis in relation to surgical shock. In collaboration with Dr. J. F. Corbett,* experimental shock is being studied at present. Here true acidosis develops, as indicated in Table VII.

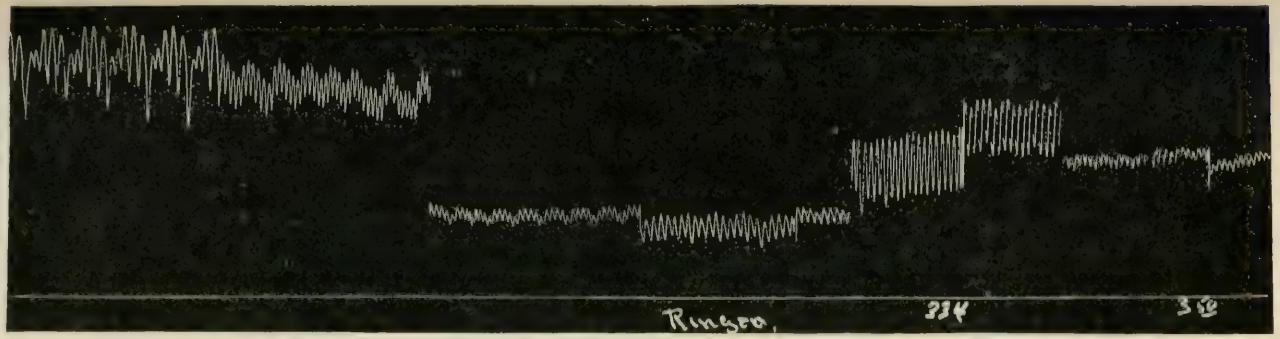
Table VII.—Shock Experiments

Dog.	Time.	Weight, kg.	pH.	Alkaline reserve.	Alveolar CO_2.	Remarks.
AE 916	9.30	25.0	7.4	43.7		
	1.30	..	7.1	38.6	27.6	
	4.30	..	7 0	28.4	32.8	
AE 913	8.30	21.8	7.4	54.6	40.9	
	4.30	..	7.0	32.1	37.1	
AE 926	9.30	25.0	7.45	51.7	43.9	
	12.30	..	7.3	..	22.6	
	3.30	..	7.1	32.1	25.6	
AE 911	9.30	18.6	7.5	51.6	48.3	
	12.30	..	7.45	38.5		
	4.30	..	7.2	..	39.5	
AE 949	8.40	19.1	7.5	56.2	54.7	3.25, 150 c.c. Ringer's solution.
	3.30	..	7.3	42.9	26.4	
	4.00	..	7.1	38.0	41.4	3.30, 100 c.c. 5 per cent. $NaHCO_3$.
	5.30	..	7.4	42.0		
30	8.30	24.0	7.45	52.9	56.5	3.03, 200 c.c Hogan's solution.
	3.03	..	7.35	28.9	26.8	
	3.22	..	..	39.3	40.8	3.22, 200 c.c. Hogan's hemolized.
	4.05	..	..	46.5	47.9	

The effect of $NaHCO_3$ upon blood-pressure in shock affords additional evidence of the existence of acidosis. Tracing I is a chemographic tracing showing the fall of blood-pressure accompanying shock and the response to the administration of $NaHCO_3$. The effect of Ringer's solution is also indicated. Tracing II demon-

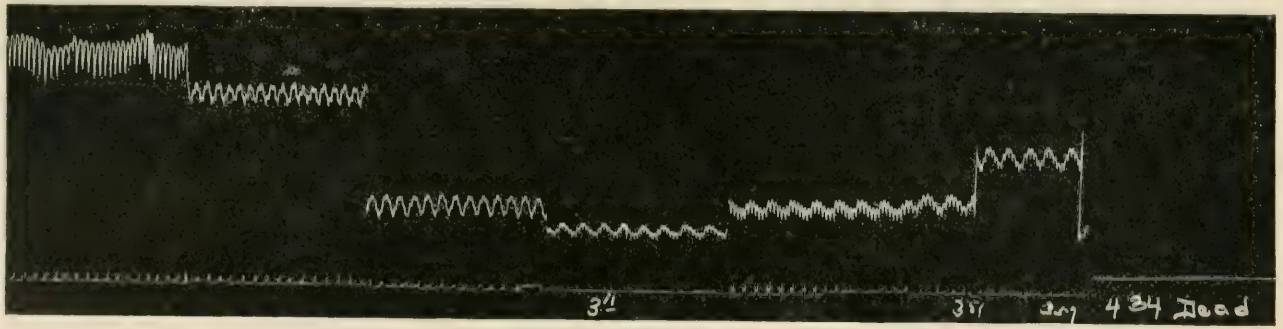
* Separate report will appear later.

TRACING I — DOG NO. 949. WT. 42 LBS.



Normal tracing at 8.40 A.M. Five per cent. bicarbonate used.	Trauma, 8.55 to 9.30, 10.35 A.M.	Trauma, 15 min. at 15 min. intervals, 2.00 P.M.	After Ringer's solution, 150 c.c., 3.25 P.M.	After bicarbonate solution, 100 c.c., 3.34 P.M.	3.50 P.M.

TRACING II — DOG NO. 30. WT. 54 LBS.



Normal tracing at 9.30 A.M.	Trauma, 11.55 A.M. to 12.20, 1.00 P.M.	Trauma, 2.45 to 3.00, 3.05 P.M.	After Hogan's solution, 80 c.c., 3.11 P.M.	After Hogan's solution, 120 c.c., 3.17 P.M.	After Hogan's solution, 200 c.c., 3.51 and 3.57 P.M.	Death, 4.34 P.M.

strates the effect of Hogan's gelatin alkaline mixture in experimental shock.

Acidosis in Starvation. It is a common belief that starvation results in acidosis. That acidosis may occur is not denied, but as the result of study of starvation dogs we feel convinced that the role of acidosis is extremely slight. Here, again, ketonuria is the more marked feature. From an uncompleted study now in progress in my department by Dr. Northington and Dr. Grave* it appears that the role of acidosis is almost negligible for ten days at least in starvation. Ketonuria usually develops within forty-eight hours and its presence has been construed into evidence for acidosis. Alkaline reserve, alveolar CO_2, and pH of the blood remain normal for the first ten days but later the alveolar CO_2 indicates a slight tendency to decreased tension.

Treatment of Acidosis. Alkali treatment is always indicated in acidosis, because a diminution in bicarbonate reserve as pointed out, by L. J. Henderson, is an invariable accompaniment of acidosis regardless of other coexisting changes. The degree of the acidosis should be determined preliminary to the administration of alkali, since the degree of acidosis controls the intensity of treatment. The more severe the acidosis the more alkali is indicated. Alkali should be administered at least until the pH of the blood returns to normal. It is desirable, perhaps, to correct the alveolar CO_2 and alkali reserve as well, although this is not always so readily accomplished.

When the treatment is intensive, alkalosis results, a condition but little studied and little understood. Chart I† illustrates the gradual development of acidosis and of alkalosis as the result respectively of slow administration intravenously of $\frac{N}{2}$ HCl of 5 per cent. $NaHCO_3$. Death resulted in both instances.

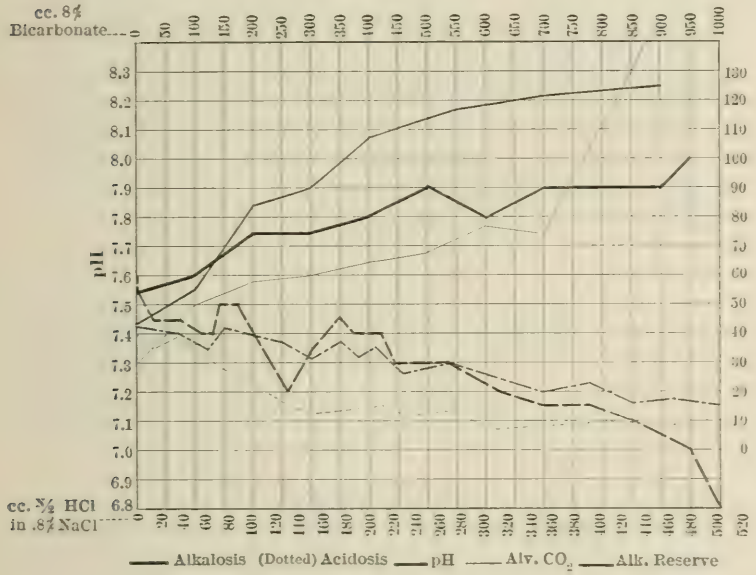
The usual clinical effects of alkaline treatment are relief of dyspnea, diuresis, with occasionally mental improvement. With lethal amounts of alkali coarse tremors and rigidity develop, and finally vomiting, convulsions, and relaxation of the sphincters. Rigor mortis is immediate and extreme.

* To be published later.

† In alkalosis the CO_2 of blood and of the alveolar air are widely divergent.

Clinically, at times, edema and ascites develop during alkali administration. Aside from alkali therapy alkalosis is rarely encountered. Levy and I have found it only in the following conditions: typhoid following transfusion in primary and secondary anemia, and in nephritis. Wilson and Stearns[26] demonstrated its presence in experimentally induced tetany in dogs.

CHART I



At the present time it must be admitted that our knowledge of acidosis is not profound. Relatively simple methods of determining its existence and intensity are now available, the same methods serving for the control of therapy. Through their use a deeper understanding of acidosis must result. More exact, and therefore more effective, treatment can be confidently anticipated.

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GENERAL DISCUSSION OF ACIDOSIS, INCLUDING PAPERS OF DRS. HOWLAND, WOODYATT, FROTHINGHAM AND ROWNTREE, OPENED BY DR. LAWRENCE J. HENDERSON AND CLOSED BY DR. YANDELL HENDERSON

Dr. Lawrence J. Henderson said that the speakers had been too kind in their appreciation of his theoretical, and *a priori*, remarks. But more than one of these ideas have been proved true; therefore there must be, at least, something of truth in the underlying theory. At any rate it is clear that in a great variety of diseases there is a diminution of ability to protect the blood against acids; and this condition, as the one known pathological change common to all these conditions, ought to be called acidosis. He wished to say, further: (1) that alkalies have been abused is no reason for refusing bicarbonates in small quantities and over long periods: for bicarbonate is, in respect of concentration, the *third* constituent of the blood: (2) while acidosis cannot be held to be the cause of disease, it can be held to be the cause of symptom-complexes in disease; for one, he believes that acidosis is the cause of diabetic coma. It is possible to overcome the acidosis of diabetic coma without curing the condition, as had been pointed out. This may be due to the fact that the cells of the body are not so readily and quickly influenced by substances introduced into the blood in treatment, even if they are accessible at all; and evidence of acidosis may disappear from the blood while the condition persists in the tissues. Some of the effects of acid are probably not accessible by the action of alkali.

Like nitrogen equilibrium and heat equilibrium the equilbrium between acids and bases is one of the fundamental conditions of life in the human organism. None of these equilibria, indeed, is free from fluctuations; in the exchange between the organism and the environment these may be wide; but such fluctuations within the body are necessarily restricted, and so far as physicochemical conditions, like temperature and the degree of alkalinity, are concerned, they are restricted within narrow limits. Nevertheless, disturbances of the acid-base equilibrium, like disturbances of the body temperature, are among the most common of pathological phenomena and they may occur in many different diseases.

Any modification of the normal equilibrium between acids and bases within the organism whereby the power to neutralize acid is diminished is to be regarded as a condition of *acidosis*. Such a condition need not, and in nearly all cases certainly does not, involve an acid reaction of the blood, or the presence of free acids, except such as may normally occur in the free state; but it involves *some change in the normal equilibrium* and diminishes the power of resisting acid.

Such changes may come about in a great variety of pathological conditions, and they may be readily produced by different experimental means. Thus the ingestion of acids or of bodies which are converted into acid products in the metabolism; a diminution in the alkali of the food; the production of abnormal acid products of metabolism; or the failure to eliminate acid from the body may all lead to a state of acidosis. But the consideration of these special causes of acidosis has little to do with the general problem, and I shall not undertake to discuss any of them.

Whatever their origin, all states of acidosis are essentially alike; they have a common physicochemical basis. This does not necessarily consist in or involve an increase of the concentration of ionized hydrogen in the blood, for the constancy of this concentration may be preserved through the action of the lung in eliminating an abnormally great quantity of carbonic acid from the blood. Indeed, the importance of the hydrogen ion at any rate as a means of investigating physiological phenomena, has been overestimated, because it has been understood that the problem of acidosis is a physicochemical problem.

What is essential and common to all conditions of acidosis is a depletion of the alkali of the body. This involves at least a diminution of the bicarbonates of the blood, and in severe cases it probably involves the draining away of large quantities of alkali from many other sources.

Nothing is simpler than the process by which this condition is established. If an acid is poured into an aqueous solution of carbonic acid in equilibrium with the air, to which a certain amount of a bicarbonate has previously been added, the acid will react, according to its concentration and avidity for base, to a greater or less degree with the bicarbonate, forming in due amounts its own salt and free carbonic acid, which must escape into the

air, since the solution is already in equilibrium with the carbonic acid of the atmosphere. Thus, for instance, a solution of sodium bicarbonate to which half of the equivalent amount of hydrochloric acid has been added will in the course of time contain just as much free carbonic acid as it did before and just half as much bicarbonate. Now the laws governing the equilibria between acids and bases determine the fact that it is in like manner chiefly bicarbonates which react with acids introduced into the blood, and when the resulting carbonic acid has been liberated by the lung the result is very similar to that of the simple chemical experiment. It is to be observed, however, that the respiratory process tends, under these circumstances, to eliminate more than the newly liberated carbonic acid; the tension of carbonic acid in the blood is thus diminished nearly in proportion to the diminution of bicarbonates, and since the hydrogen ion concentration is proportional to the ratio of the free carbonic acid to the bicarbonates, the degree of alkalinity of the blood is unchanged by the introduction of acid, hence the theory that the hydrogen or hydroxyl ion is the hormone of respiration, *but the equilibrium is changed*. The process, however, does not stop here, for this equilibrium engages in all the other acid-base equilibria of the body, and accordingly alkali is yielded up by alkaline phosphates to form acid phosphates and fresh bicarbonates, other alkali is split off from proteins, and still other reserves of alkali are probably mobilized. The analysis of such processes is a highly complex affair. But in all cases the process involves *at least* a diminution of the bicarbonate of the blood. This condition is therefore the essential indication of the condition of acidosis. It may be readily detected either by measuring the capacity of the blood for carbonic acid or the retention of alkali administered by the month, according to the simple method introduced by Sellards and by Palmer and myself. The estimation of the alveolar carbonic acid is also useful.

Normally these processes are counterbalanced by the elimination of an extremely acid urine and by the production of a great quantity of ammonia. But pathologically neither of these conditions is a constant accompaniment of acidosis, and neither is a sure basis for conclusions.

The condition of acidosis, simple though it may be in its essential features, is physiologically of the greatest complexity; for the acid-base equilibrium is involved in a great variety of other equilibria, such as those of osmotic pressure and volume; it influences the distribution of electrolytes between corpuscles and plasma, the state of colloids, hence perhaps the union of oxygen and hemoglobin; it modifies the activity of enzymes; and it is probably involved in many undiscovered phenomena. It modifies, moreover, the general metabolism and the activities of lung and kidney. Here are problems enough to occupy many years of research, and I have no doubt that the results of these researches will advance the science of medicine. There is a tendency, however, to generalize from incomplete information and inadequate physicochemical analysis of some of these phenomena,

and thus to arrive at theories and practices which are sometimes far from certain, except in respect to their harmfulness. And for this reason I feel obliged once more to declare that I know of nothing which indicates that acidity or a tendency to acidity is the cause of edema or nephritis. And I feel bound to urge the medical profession to great caution in dealing with these difficult questions.

On the other hand, nothing is simpler than to treat most cases of acidosis, except those of the diabetic type, with moderate doses of soda. For this purpose the reaction of the urine seems to be a safe guide, and I feel confident that an individual whose urine is kept nearly neutral to litmus and not strongly alkaline will ordinarily be quite free from any ill effects of acid and not liable to the ill effects of excess of alkali, as they undoubtedly appear in nephritis. Such treatment depends upon the fact that acidosis always involves a diminution of the bicarbonates of the blood, and that this cannot persist in an individual whose urine is continuously neutral. In that this condition is one of the most common of pathological states, it is fair to suppose that the therapeutic use of soda should be one of the most frequent prescriptions of the physician.

Dr. E. P. Joslin, Boston, acknowledged his debt to Dr. Henderson for the simplicity of his exposition of this subject. He referred also to the clarity of Dr. Woodyatt's exposition of the dependence of the acidosis of diabetes on defective utilization of carbohydrates. Two-thirds of all diabetics die in coma; and all diabetic children. Eighty-seven per cent. of all diabetics, dying in the first year of the disease, die in coma. If it can be shown that the number of diabetic fatalities in the first year of the disease has been lessened, this must be because the treatment of acidosis has improved with the improved treatment of diabetes. Such statistics are now available and do show that the mortality of diabetes in the first year has been greatly reduced. Clinicians can congratulate themselves on this distinct advance in the treatment of a difficult disease.

Dr. C. F. Hoover, Cleveland, said that one point bearing on the relation between acidosis and CO_2 tension of alveolar air needs to be emphasized: there seems to be an impression that there is a definite relationship between CO_2 tension of alveolar air and the amplitude and rate of ventilation. There is no such definite constant relationship, and he cited cases to show this: cases of hyperpnea without acidosis, and cases of acidosis with hypopnea.

Dr. D. D. Van Slyke, New York, said that in studying the relations between the kidney, lung, and blood functions in acidosis he had been struck by the beautiful concord between the clinical and chemical facts, and the theoretical considerations advanced originally by Dr. Lawrence Henderson. He agreed with Henderson that acidosis is best defined as

and detected through the decrease in the bicarbonate of the blood caused by retained acids. He emphasized the fact, pointed out by Rowntree, that genuine acidosis can occur without increase in the H-ion concentration of the blood. As a matter of fact this does almost regularly occur in diabetic acidosis. The "uncompensated" acidosis, with actual increase in H-ion concentration, sets in only when respiration fails to reduce the free carbonic acid of the blood in proportion to the reduced bicarbonate. In diabetes and, also, as shown by Peabody, in nephritis this is likely to occur only in the final stages of acidosis, when terminal coma approaches.

The CO_2 tension of alveolar air owes its significance to the fact that it is an indirect measure of the bicarbonate concentration of the blood. It is proportional to the blood bicarbonate, however, only when the lungs and circulation are functioning in an entirely normal manner. Similarly, certain urinary changes are recognizable and acceptable as indirect evidences of acidosis; but they are not synonymous with acidosis, and they depend upon renal integrity and other factors for constancy. Both theoretical consideration and practical experience indicate the desirability of diagnosing acidosis on direct determinations of the blood bicarbonate.

Dr. H. A. Hare, Philadelphia, said he naturally felt somewhat timid about speaking as a clinician after men so respected in the biochemical and physiological fields. Dr. Janeway had alluded to the attenuated atmosphere at the altitude reached in the discussion; but he reflected that the navigator derives much useful information from the astronomer without seeking the astronomer's glory. He had hoped to learn how to apply what was said here to the treatment of acidosis of whatever type, but he confessed to disappointment, except in the matter of the use of alkalies. Thirty years ago he had learned in Ludwig's laboratory that the blood is the most carefully protected tissue of the body, and that one should be careful to do no harm by introducing strange substances into it. This warning should be heeded in view of what has been said here about the harmful effect of too active alkali therapy in acidosis. This Association has a grave responsibility to the practitioners of the country, and he cited instances of the indiscriminate use of alkalies on the strength of statements made before this organization. He added that while he had not been able to follow the Allen treatment entirely in the management of diabetes, he had learned not to be so alarmed as formerly at the appearance of acetonuria during the course of starvation.

Dr. S. J. Meltzer, New York, said he felt a great obligation to the president for the symposium and especially for inviting both Drs. Henderson to discuss the subject. I appreciate the lucidity of Dr. Lawrence Henderson's statement. The Association should especially appreciate it because another president had invited another investigator who made the

sweeping statement that many ills are due to acid, and all such ills can be cured by alkalies. Dr. Henderson's clear-cut statement atones for this: under his simple exposition the mode of equilibrium of the two factors in the blood, acidosis and alkalinity, becomes intelligible.

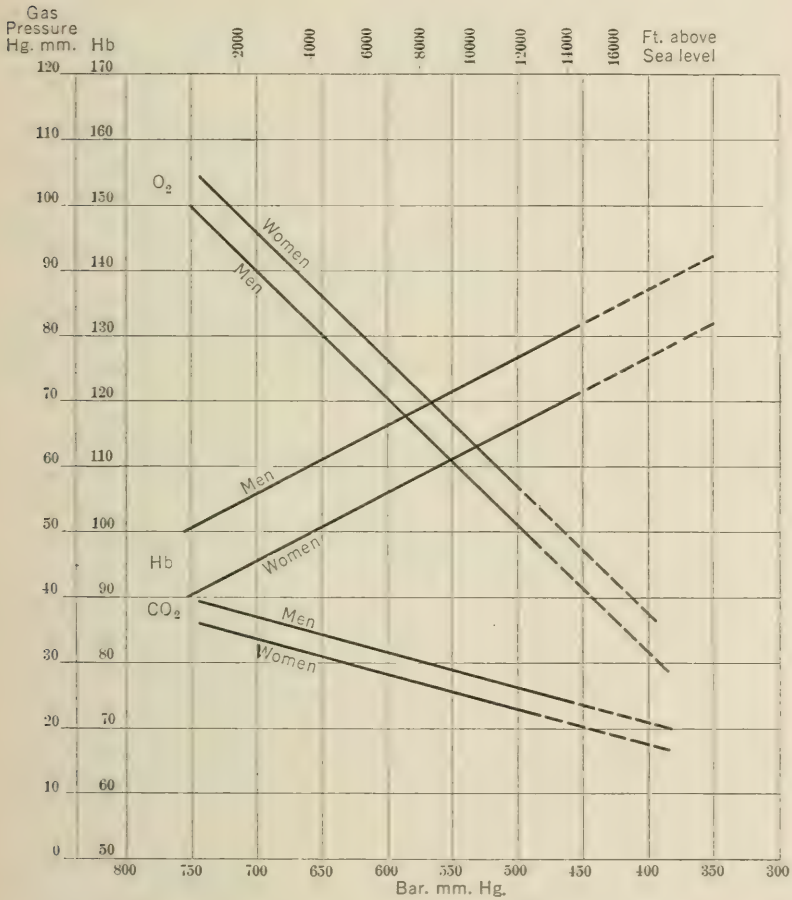
Dr. Theodore C. Janeway, Baltimore, said he wished to discuss the subject on a sea-level basis; he would not seek to attain the altitude of Dr. Yandell Henderson's remarks. The discussion had been very valuable for clearing the views of clinicians and pathologists alike. Thus far we have talked of acidosis in terms of ketonuria, but it has now been shown that the modern conception of acidosis, acidosis in its strict sense, is the true cause of diabetic coma. Most of the criticisms have been made on the fact that acidosis is merely a biochemical event and not a just measure of disease; but it is the acidosis that causes the hyperpnea, etc., and it is possible to conceive of acidosis as the cause of functional disturbances without sacrificing the truth of Lawrence Henderson's remarks about the non-specificity of the blood changes in this condition. The newer types of acidosis have to be recognized: it is only necessary to remember that there are fundamental metabolic differences in the origins of the various types.

Dr. Yandell Henderson, New Haven, said it seemed important first to inquire whether all of the previous speakers under the general title "acidosis" were talking about one and the same thing. It seemed to him that they were not.

The first paper, that of Dr. L. J. Henderson, presented a clear-cut scientific picture of a physicochemical balance. In the other papers the speakers were dealing with clinical conditions involving this balance complicated with other factors in addition. This is often the difficulty in the study of medical problems. We need a simple and clear-cut nomenclature, but we must not let this precision of definition blind us to the fact that actual clinical conditions are not equally simple and clear-cut. The acidosis which we used to talk about—the acidosis of high ammonia and oxybutyric acid in the urine—is certainly not in all respects identical with the acidosis of today, which is concerned with the respiration and the blood. The acidosis of diabetes is not identical with the acidosis of asphyxia nor of nephritis. It would be truer to the facts in one case to speak of "ketonosis," in another of a state of low alveolar CO_2, and in a third of an altered buffer value in the blood. Doubtless acidosis in the pure scientific sense is involved in each of the conditions thus specially characterized, but clinically each includes also other elements.

In 1911 he had been a member, with Dr. Haldane and others, of the Pike's Peak expedition. All of the party developed and maintained throughout their stay at the summit of the Peak a marked condition of acidosis, as shown by the lowering of the CO_2 tension in the alveolar air. During the

same summer it was shown by a party on Monte Rosa, as well as by corroboratory evidence obtained on Pike's Peak, that at great altitudes the blood becomes meionectic. It is to be remembered that it was by means of meionexy and a lowered alveolar CO_2 that Thomas Lewis, Barcroft and their co-workers first demonstrated the acidosis of renal origin in which there is now so much interest. Renal acidosis and the acidosis in a normal individual at a great altitude are apparently practically identical, but this acidosis presents marked points of difference from diabetic acidosis.



He expressed himself as rather skeptical of the hurtful effects of acidosis *per se*, for none of the figures reported in the papers in this symposium indicated a more severe acidosis than he himself and the other members of

the party persistently maintained throughout their stay on Pike's Peak (14,000 feet), yet they felt very well indeed. In fact, to a considerable extent the process of becoming acclimated to altitude and the benefits of a trip to the mountains consist in the development of a certain degree of acidosis.

The description of acidosis given by Dr. L. J. Henderson was on the basis of sea-level data. Miss Fitzgerald, in connection with the Pike's Peak expedition, has shown, as the result of hundreds of observations made by her at various altitudes, that acidosis is not something which suddenly develops at a great altitude. On the contrary, for each barometric pressure there is a certain normal degree of acidosis, and as the altitude is increased and the mean barometric pressure falls, the normal non-volatile-acid-alkali equilibrium alters accordingly. The evidence available indicates that residence under compressed air in a caisson would normally lead to the development of an alkalosis. The net result of Miss Fitzgerald's work is that the altitude of any city or town in the world can be determined by measuring the CO_2 tension of the alveolar air of the inhabitants, or, in other words, by their mean normal acidosis. The same thing holds true of the mean normal hemoglobin content of the blood.

Miss Fitzgerald's results are summarized in the accompanying diagram:

Acidosis is not itself a disease, but is like fever, an incident of disease. Alkali therapy for acidosis is certainly beneficial, but like the treatment of fever with ice it is merely symptomatic.

In view of the misrepresentation of this topic by a certain surgeon (Crile), it is to be emphasized that except in extreme conditions the blood in acidosis is not appreciably more "acid" than normally. The alkaline elements are diminished or the non-volatile acids are increased, but the respiratory mechanism automatically effects a counteracting decrease in the carbonic acid of the arterial blood so that the H-ion concentration is held at nearly the normal value. The volume of breathing is increased and the power to hold the breath diminished. As the sodium bicarbonate of the blood is further reduced dyspnea becomes extreme, the breath cannot be held for even a few seconds, and coma and death follow.

Particularly in diabetes a daily testing by the patient himself of the length of time that he can hold his breath without considerable effort after a moderate inspiration may afford an early warning of an increase of acidosis.

THE PHYSICAL SIGNS AND SYMPTOMS OF WOUNDS OF THE CHEST*

By C. P. HOWARD, M.D.
IOWA CITY

From August 7 to November 1, 1915, there were admitted 3039 to the hospital to which the writer was attached, of these 1315 were sick and 1724 wounded; of the latter 107 (6 per cent.) received either a gunshot wound or shell wound of the thorax. Twenty cases were evacuated too rapidly to permit of a physical examination of the chest. This leaves 87 cases for purposes of analysis.

Forty-five were the result of gunshot wounds, and of these 41 penetrated the thoracic cavity; the remaining 4 were merely wounds of the parietal wall without obvious penetration of the pleural cavity.

Forty-two were the result of shell wounds of some kind, as high explosive, shrapnel, trench mortar, or hand grenades. Of these 28 had certainly penetrated the chest wall and 14 had apparently not, though 1 at least had caused a fracture of a rib which had lacerated the pleural cavity.

These cases we shall divide into four groups for purposes of description and consideration.

Group I. Fifteen patients presented no abnormality in the lungs or pleuræ at the time of the examination. That is to say, 17.2 per cent. of wounds of the chest revealed no injury to lung or pleura a few days after the receipt of the injury, and that in spite

* I wish to express my appreciation to Col. Birkett, Lieutenant Colonels Elder and McCrae, Majors Hill and Archibald and the other officers of No. 3, Canadian General Hospital, for the opportunity to see the cases and for permission to publish them.

of the fact that of these 6 were penetrating gunshot wounds and 1 penetrating shell wound. The remaining 8 had only affected the parietal wall.

Group II. A very interesting group of 6 cases comprised 4 cases of pneumonia and 2 of serous pleurisy with effusion. The 4 pneumonias all resulted from shrapnel, 2 of which were penetrating wounds. Further, what was of special interest in 2 cases, the involvement was on the side opposite to the wound. A third case was a double pneumonia associated with paralysis of the vocal cord from a missile lodging in the upper right chest behind the first rib, and was possibly originally an aspiration pneumonia. The fourth pneumonia patient had only a small shrapnel wound of the thorax but was buried in a trench for some time and consequently much bruised about the thorax. One of the pleurisy with effusion cases had an accompanying pneumonic consolidation of the lung resulting from a non-penetrating gunshot wound of the opposite side. The other case was a simple serous effusion the result of a non-penetrating shell wound of the same side.

Group III. This includes 1 case of mediastinitis resulting from a rifle bullet lodging in the anterior mediastinum. The only symptoms complained of were pain referred to the right side of the neck over the upper and outer border of the trapezius muscle and slight dysphagia. On inspection there was a marked area of ecchymosis over the manubrium, but, of course, as yet no fulness of the superficial veins. There was in addition a non-fluctuating, elevated tender area beneath the discolored skin from the subcutaneous hemorrhage. There was a definite area of dulness corresponding to the anterior mediastinum, reaching above to the upper margin of the manubrium, below merging with the heart dulness, extending to the right about 1 cm. beyond the sternal border and to the left just to the sternal border. On auscultation over the manubrium and raising the patient's arms above his head there was a well-marked grating friction, a sign described by Perez[1] and reported by the writer[2] in other cases of mediastinitis. A skiagram revealed a sharply pointed bullet slightly more than one inch in length lying apex downward behind the manubrium, to the right of the mid-line, one inch from the surface.

Group IV. Comprises the hemothorax cases which for purposes of discussion have been further subdivided into the infected and sterile.

A. Infected Hemothorax. Of the 65 cases, 9 were definitely infected (13.8 per cent.). This is a somewhat lower percentage than that given by Col. Sir John Rose Bradford[3] in his series in which 25 per cent. of 328 cases were infected. Hale White[4] found only 10 per cent. of the cases with evidence of infection of the fluid in his base-hospital experience in England.

As to the nature of the wounds, 4 were penetrating gunshot wounds, 4 were penetrating shell wounds, and 1 was a non-penetrating shell wound which had caused a fractured rib, a spicule of which had lacerated the pleura and was to all intents and purposes a penetrating chest wound. The infective organism was one of the gas bacillus group in 1 case, B. tetani 1 case, pneumoccus 1 case, streptococcus 1 case, Streptococcus and Staphylococcus aureus 1 case, and a large unidentified bacillus (recovered on three separate aspirations) 1 case. In the remaining 3 no cultures were made.

Cough, hemoptysis, pain, and dyspnea were present in about the same proportion as in the next group, under which these symptoms will be discussed in detail.

As one might expect, the temperature range was higher in this group than in the non-infected cases, and not uncommonly ran a more or less continuous curve of 103° to 104° F. This fever curve, taken in conjunction with the rapid pulse (120 to 140) and a marked tendency to polypnea (28 to 40) would always suggest the chart of ordinary acute lobar pneumonia.

In 2 cases the infection lay dormant for ten days and eighteen days respectively. In the first of these cases a penetrating shrapnel wound was received on September 25; an exploratory aspiration on October 1 revealed a bloody fluid, smears, and cultures from which were negative for organisms; a second aspiration on October 5 revealed a good many organisms of the "gas bacillus group;" a third aspiration on October 7 showed the same organism, though in smaller numbers. The second case received a penetrating gunshot wound on October 13 and ran a normal temperature, pulse, and temperature curve until October 31, when there was a sudden

rise in all three (temperature, 104.4°; pulse, 120; respiration, 28), and an exploratory puncture revealed a large bacillus morphologically resembling that of the gas bacillus group, but which grew aërobically as well as anaërobically, did not produce gas, and was unidentified, but probably belonged to the group of diphtheroids found by others in this war; that it was the cause of the infection of the pleural exudate cannot be doubted, as it was found alone on three separate aspirations.

Physical Signs. The physical signs in this group differed in no way from those of the sterile cases. We never found the two signs of anaërobic-bacillus infection described by Bradford, namely, a rapid displacement of the heart and a "cracked-pot" percussion note from the rapid development of gas within the pleura.

Only 2 of the cases showed definite signs of pneumothorax, while in a third air and pus could be seen and heard sucking in and out of a large wound in the upper back, though none of the characteristic signs of pneumothorax could be detected, but merely those of an extensive fluid exudate. This case interested me much at the time. West[5] reports 2 cases with large wounds of the chest in which the lung did not collapse, though no adhesions were present, and in which there were no signs of pneumothorax. All of us have noted the absence of signs of pneumothorax after thoracotomy for a recent empyema. On the other hand, if the empyema be of long standing and firm adhesions have formed, causing pocketing of air and pus, well-marked signs of pneumothorax may be present, as in a case seen recently in the surgical clinic (University Hospital, No. 2609). While infection should be suspected in every case which is not progressing favorably after the fourth day, it cannot be diagnosed on clinical symptoms and signs alone. An exploratory aspiration and a bacteriological examination (both smears and cultures) should be made in all suspicious cases.

As regards treatment in 4 of the cases, a thoracotomy was done, as a result of which 2 were discharged well, 1 improved, and 1 died. One case which was drained at a casualty clearing station by inserting two rubber drainage tubes between the 8th and 9th ribs in the posterior axillary line died five days later under our care. One case was merely aspirated and was discharged improved, but

whether or not he subsequently came to more radical treatment is not known. In 3 cases no surgical procedures were instituted, in 1 case because a coexisting tetanus caused death, in another because the patient was moribund upon admission; the third was evacuated to England at the patient's request in an apparently hopeless condition owing to the existence of a complete paraplegia of the lower extremities.

One striking feature of the cases in which a thoracotomy was performed was in spite of the promptness of the surgical interference, the slowness of the convalescence owing to the marked tendency in these cases to the formation of adhesions and the consequent pocketing of pus that occurred.

B. Sterile Hemothorax. This was by far the largest group, comprising as it did 56 patients; 31 were the result of gunshot wounds, of which all but 1 had penetrated the chest cavity. In 25 shrapnel, hand grenades, or some form of shell was the cause of the wound, 20 of which had obviously penetrated the thoracic cavity; in the remaining 5 no penetration wound was demonstrable and the hemorrhage must have resulted from laceration of the intercostal arteries or severe contusion of the lung itself. The four chief symptoms were cough, hemoptysis, dyspnea, and pain in the chest.

Cough was a most constant symptom, being present in 41 cases, absent in 9, and not noted in 6. In other words, it was present in 82 per cent. of cases in which a definite note was made. For the most part it was the characteristic short, sharp, dry cough of an ordinary pleurisy. Apart from these cases in which a definite hemoptysis occurred sputum was strikingly absent.

Hemoptysis was also a very constant symptom, being present in 39 cases, absent in 7, and not noted in 10. In other words, in 85 per cent. of the cases blood was expectorated. This varied from a few mouthfuls immediately after the reception of the wound to a more prolonged and repeated hemoptysis, persisting in some cases for days. Of course, in the immediately fatal cases which were not seen by us, very extensive external hemorrhage must occur in many cases. While hemoptysis is usually due to penetration of the lung with laceration of a bloodvessel, Rose Bradford[6] believes it might

also be due to an infarction of the lung from bruising when there is no proof that the missile had penetrated the lung substance. A fatal hemoptysis occurred only once in 1000 cases studied by this author.

Dyspnea was a somewhat less frequent symptom, occurring in 21, absent in 10, and not noted in 25. That is to say, it was present in approximately 70 per cent. of the cases. It was rarely marked and usually of short duration; even the cases with a small pneumothorax showed at the most slight respiratory embarrassment.

Pain in the chest was present in 24 cases, absent in 7, and not noted in 25. This means approximately 80 per cent. of the patients with a complete history complained of pain somewhere in the chest, usually at the site of the wound, though not infrequently in the axilla or front of the chest. It was always worse on breathing or on movement of any kind.

Fever of varying degree was noted in 47 patients and absent in 9 (*i. e.*, 99° or less); that is, 92 per cent. showed fever. Of these 20 patients had a temperature at one time or another of 102° F. or over, and 3 even to 104°. Another 12 had a rise to a point between 100.2° to 101.8° and 15 between 99.2° and 99.8°. The presence of fever by no means indicated an infection of the pleura or underlying lung, and was due in these cases either to an infection of the parietes or to absorption of the blood contained in the pleural cavity; the latter being analogous to the so-called protein fever of the experimental laboratory.

The pulse was accelerated in everyone of the 56 cases (100 per cent.). In 10 cases it was markedly (120 or more per minute), in 35 moderately (90 to 119 per minute), and in 11 slightly elevated (80 to 89 per minute). This was no doubt due in part to the parietal infection, but chiefly to the physical exhaustion and shock experienced by the patient, as the pulse rapidly returned to normal after proper rest in bed and suitable nourishment. Hemorrhage itself played but a minor role, and that only in a small proportion of cases.

Respirations were about normal in 43 of 54 cases (80 per cent.). They were markedly accelerated (*i. e.*, 32 or more per minute) in 12, moderately (25 to 30 per minute) in 14, and slightly (22 to 24

per minute) in 17 patients. In 13 cases the respiratory rate was normal upon coming under our observation at the base.

The physical signs were as follows:

Inspection yielded invariably a diminished movement of the affected side; in some cases this was exaggerated by the patient's apprehension of causing pain or producing a hemorrhage. Fulness was not a constant feature except in the very extensive effusions. Two or more weeks after the wound one was not infrequently struck with the subsequent retraction of the thoracic wall, more than one sees in civil life except in cases of empyemata and fibroid phthisis. This was due to the marked collapse of the lung, and according to writers in England is entirely recovered from as the lung expands from suitable exercises.

Palpation frequently reveals the characteristic crackling of subcutaneous emphysema for a considerable distance around the wound, being present in 10 of our 56 cases. This phenomenon no doubt is due to escape of air from the underlying lung and is subsequent to a transient pneumothorax, though in only 2 of these cases were the other physical signs of air in the chest present. Of course, the diminished motion could also be detected. Tactile fremitus was diminished in the great majority of cases (90 per cent.), and in the remainder it was either normal (1 case), increased (1 case), or diminished in front and increased behind (2 cases). Increase of vocal fremitus is readily explainable by the compression of the underlying lung and in our series, considering the other evidence of compression, was surprisingly rare.

Percussion. The note was usually dull in moderate effusions (30 cases) and of a woodeny flatness in the larger effusions (18 cases); in 8 no remark as to the quantity of the effusion was made. A tympanitic note was present in front or above the line of effusion in 4 uncomplicated cases, and was no doubt the Skodaic hyperresonance present in simple effusions above the level of fluid. In 3 other cases, however, the tympany was associated with other suspicious signs of a pneumothorax. In 8 additional cases the tympany occurred in conjunction with other more definite signs of a pneumothorax.

Rose Bradford called our attention to the frequency of an atonic

relaxation of the diaphragm so that the area of gastric tympany was found to extend unusually high on the left side; this phenomenon he does not believe to be due simply to a wound of the lung, for it only appears with hemothorax.[3] We examined for it in too few cases to express an opinion as to its value.

Auscultation. The breath sounds were for the most part suppressed or absent (30 cases), but in 19 other cases (39 per cent.) they were noted as bronchial over the back or above the line of effusion. This again shows the frequency and extent of compression of the lung. In 7 cases no note was made as to the character of the breath sounds. The vocal resonance, as determined by the transmission of the spoken voice sound with the aid of the stethoscope, was increased in 11 cases, diminished in 12, and normal in 1 case. In the remainder no note was made. Here, again, we find evidence of the frequency of compression of the lung.

The transmission of the whispered voice sounds (pectoriloquy) was only tested for in 5 cases, but was present in 4 of these.

Medium or fine moist rales were noted only 7 times in spite of the frequency of compression of the lung. A pleural friction was more frequent, being present in 12 cases, in 3 of which it had the pleuropericardial character.

There were 8 cases of undoubted pneumothorax and 5 suspicious cases, and yet a metallic tinkle was heard in only 6 cases and the coin sound or "bruit d'airain" of Trousseau in 4. The Hippocratic succussion was not tested for, owing to the importance of keeping the patients as quiet as possible.

Cardiac displacement was a very constant sign, being present in 23 cases of 32 (72 per cent.), in which a note was made as to the position of the heart. We were much struck with the degree of displacement even when the effusion was relatively small in amount, and considered it to be further evidence of the probable frequency of the existence of a pneumothorax in the early stages of the thoracic injury. The greater density of the fluid as compared with that of ordinary serous effusion did not satisfactorily explain the greater displacement of the heart in these cases. The heart very slowly returned to its normal site even after the effusion had largely

subsided, and in many cases the patient was sent to England with considerable cardiac displacement persisting.

X-ray Findings. In only 20 cases was a skiagram taken, (1) as in the cases with a wound of exit it was unnecessary, (2) as we moved our patients as little as possible. In 12 of these cases the missile was located in the thorax, in 1 case it had penetrated the diaphragm and had come to rest in the abdominal cavity. In the other 7 cases no foreign body could be found. In 3 cases fluid was still present when a search was made for the foreign body. In 1 other case a pneumothorax still existed.

Complications. In 2 cases there were undoubted signs of fluid on the two sides of the chest and in a third case there were signs of either a small effusion or a marked displacement of the posterior mediastinum and its contents.

As was noted before, there were 8 cases of undoubted *pneumothorax* and 5 in which there was more than a strong suspicion. The majority of these cases were admitted within a day or two of one another after the British offensive of September 25 and 26, 1915, when the wounded were evacuated very rapidly to the base. Further, the signs of air in the chest rapidly disappeared, in several instances in twenty-four hours. The greater incidence in those seen shortly after being wounded and the rapid absorption of the air under observation lead us to believe, with all due respect to the opinion of Sir John Rose Bradford,[3] that a mild form of pneumothorax is a common occurrence and must be present in the majority of cases in which a missile has penetrated the lung. It is of interest to know that Otis[6] noted in the American Civil War not more than half a dozen cases in which a pneumothorax was a troublesome complication. We must admit with Rose Bradford that over an area of cutaneous emphysema the character of the percussion note may suggest the presence of a pneumothorax when none is present. Rose Bradford found only 12 cases of pneumothorax in 500 patients with wounds of the chest and in only 5 was its presence proved. Hale White found only 2 cases of air in the pleural cavity in the 50 cases seen by him in England. Naturally the amount of air that escapes is very small if the missile be a high-velocity bullet from a rifle or machine gun, and consequently is overlooked unless

carefully examined for within forty-eight hours or so after the reception of the wound. Further, of course, there is seldom if ever a valvular opening such as one sees in a pneumothorax due to tuberculosis. As shown in several autopsies of the infected hemothorax group there is at once a sealing of the opening in the lung substance by fibrin, which effectually prevents further escape of air. In 1 case the fibrinous plug had been inflated like a small balloon by the air in its attempt to escape from the damaged lung. Lastly, Osler[6] has pointed out the metallic phenomena which are the most striking signs of air in the chest are best heard in cases with a consolidated lung and thickened pleura. Distention, immobility, lack of vocal fremitus, hyperresonance, and absence of breath sounds and displacement of viscera are the signs of a pure pneumothorax, and can readily be confounded with those of an extensive effusion.

Lobar pneumonia was present in 4 cases, in all on the side opposite to the wound and the subsequent hemothorax. These 4 cases together with the 2 mentioned in Group II give a total of 6 cases in our series in which all the physical signs and symptoms of a pneumonic infection existed in the side opposite to the injury. While trauma is a well-recognized cause of pneumonia since the days of Litten, who found a history of 4.4 per cent., I can find no mention of the opposite lung being involved in the current text-book and monographs. It is difficult to understand the pathogenesis of a pneumonia by "contre-coup." Rose Bradford noted that hemothorax and pneumothorax might be found in the side opposite to the wound in the chest when the bullet penetrated the lung transversely. He noted that contralateral pleurisy was commoner in the cases infected with streptococci; he further admits that pneumonic consolidation does occasionally occur in the contralateral lung[3] but never in the side of the hemothorax.

A secondary hemorrhage into the pleural cavity is an exceedingly rare event if the patient be kept completely at rest for several days after his injury. In some cases it is said to have been the cause of death when attempting to transport the patient to the base too early. In 100 autopsies reported by Henry[6] death was due to hemorrhage in only 8.

Pt. Private D. J. B., Reg. No. 16691, was admitted to our care forty-eight hours after receiving a shrapnel wound of the right chest in the third interspace anteriorly; on admission, in addition to signs of a moderate hemothorax, there were undoubted evidences of pneumothorax; four days later, during which time he had been kept strictly at rest, he became extremely pale, the pulse became very rapid and thready, and the respiration became more rapid and labored. The diagnosis lay between a virulent infection of the hemothorax, as described by us above, or a secondary hemorrhage. The whole picture was more suggestive of the latter; however, to make certain, an exploratory needle was introduced and a few cubic centimeters of blood, which clotted in the syringe, were removed. That the blood was clotted was proof of the recent occurrence of the hemorrhage, as the bloody exudate usually removed by aspiration or drainage shows little or no clotting *in vitro*. Further, the smears and cultures were negative, and the patient gradually recovered, with merely supportive treatment and absolute rest.

A case of cholehemothorax has been reported by Elliot and Henry[11] from a fistula between the liver and pleura following a bullet wound.

In 3 cases there was a simple fibrinous *pericarditis*, as evidenced by the presence of a pericardial friction. In 2 of these cases the wound was in the left chest. In another patient who had received a gunshot wound of the chest, the bullet having entered at the left nipple and passed out at the right nipple, there were signs of fluid (namely a triangular area of absolute cardiac dulness and, distant heart sounds) with the subsequent development of a to-and-fro pericardial friction, all of which were very suggestive of a hemopericardium.

In still another case there were the characteristic signs of a *pneumopericardium*. As I hope to report the case at some length in the near future, suffice it to say that the patient received a shell wound of the lower left posterior aspect of the chest; the missile must have penetrated the diaphragm as well as the pleura, with the production of a subdiaphragmatic abscess. Two weeks after the receipt of the wound he developed sudden dyspnea, rapid pulse, precordial tympany, absence of heart sounds, and the presence of a most remarkable to-and-fro churning, musical, echoing sound

synchronous with the systole and diastole of the heart and persisting upon holding the breath. Some days later, after the air was absorbed, a dry pericardial rub became audible.

Twelve cases were complicated by extensive *infection* of the tissues from wounds for the most part other than those about the chest. In 2 cases the patient nearly succumbed to a secondary hemorrhage from the invasion of one of the main arteries of the upper or lower extremity. The case of the subdiaphragmatic abscess has already been referred to.

TREATMENT. In the majority (70 per cent.) of the cases, apart from absolute bed rest and a bland nutritious diet, no treatment was necessary, the bloody exudate being absorbed usually at the end of fourteen days after the reception of the wound. In 3 cases in spite of the presence of signs at the expiration of two weeks an exploratory aspiration was negative. In 5 other cases an exploratory aspiration revealed sterile bloody fluid, but the withdrawal of a few cubic centimeters sufficed to promote absorption. In another 5 cases amounts varying from 400 to 1600 c.c. were removed. This fluid was withdrawn slowly by means of an ordinary Potain aspirator without causing any outward symptoms. It never reaccumulated. The fluid itself varied in color from an ordinary deep scarlet to a deep chocolate; it was usually thin but sometimes of a syrupy consistence, and on standing showed little or no clotting. Only in one instance was an appreciable amount of fibrin noted. The postmortem examination of 1 case in this series and in several of the infected cases readily explains the absence of clotting *in vitro*, as the visceral and parietal pleuræ were covered by thick fibrin which had evidently separated out *in vivo*. This fibrin not infrequently plugs the lumen of the needle, unless a large one (preferably a trochar) be used. Upon standing a sediment of red cells in various stages of decomposition with an occasional leukocyte can be found.

Henry[6] believes that primary coagulation of the effused blood and a deposition of fibrin occurs in a few hours; afterward exudation of lymph may occur which will induce secondary clotting. Denny and Minot[11] offer experimental proof that the blood remains fluid

in the pleural cavity, not because of any alternation of its elements, but because of previous coagulation and defibrination. Following the suggestion of Colonel Sir John Rose Bradford, 2 cases of extensive simple hemothorax were treated by aspiration and oxygen replacement. We used a simple home-made manometer and the oxygen tank of the Clarke oxygen-ether apparatus, introducing two needles into the chest, one for aspiration and one for the oxygen to enter. An attempt was made to keep a constant pressure equal to that noted before the withdrawal of any fluid. Of course the resultant pneumothorax persisted for two or three days and this gradually disappeared. We see no reason why all cases could not be aspirated early if this proceedure be used (let us say on the sixth or seventh day), without giving rise to secondary hemorrhage, as was experienced by the physicians of the Royal Army Medical Corps in the South African War.

Prognosis. Of the 87 cases only 6 died (6.9 per cent.), and of these 6 cases, 4 were infected hemothorax, 1 died as the result of multiple amebic abscesses of the liver, with local peritonitis, and 1 from an infected bullet tract in the lung. That is to say, approximately 8 per cent. of our hemothorax series died, which approximates very closely the mortality of Rose Bradford's series. In the latter's series of about 450 cases 10 per cent. died from sepsis, 5 per cent. from hemorrhage, and others from sundry complications.

In our series 69 were discharged well (79.3 per cent.), 11 improved (12.6 per cent.) and on the high road to recovery; 1 was sent to England unimproved because of a coexisting paraplegia of the lower extremities. These encouraging figures, of course, hold true for only those cases which are removed from the battlefield and are eventually evacuated to the base. Many wounds of the chest must be fatal within a short time. As to what is the proportion of these we have as yet no figures to guide us. The ultimate prognosis of wounds of the chest, according to Hale White, seems to be good, for it is not uncommon to see such cases returned to the firing line. Convalescence is necessarily slow, but the flattening of the chest in the course of several months almost disappears.

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DISCUSSION

Dr. David Riesman, Philadelphia, said that he had noticed the same peculiar physical signs described by Dr. Howard in 2 cases of hemothorax due to traumatism without penetration of the chest wall. The cases recovered spontaneously by absorption of the blood.

A STUDY OF THE DIET IN DISPENSARY PATIENTS[1]

By FRANK A. CRAIG, M.D.

AND

H. R. M. LANDIS, M.D.

PHILADELPHIA

In the study of any disease it is extremely important to determine not only the direct, immediate mode of infection, but also to carefully consider all the factors which may predispose the individual to the infection. This is peculiarly true in the study of tuberculosis which apparently requires for its growth and development a lowering of the resistance of the individual. This decrease in the resistance may be brought about by some other disease, dissipation, injury, or may result from a lowering of the general vitality resulting from hard work or faulty mode of living. Every plan suggested for the eradication of this disease must be considered incomplete and ineffectual which does not recognize the importance of these contributory or predisposing factors and include in its scheme some provision for their correction or suppression.

Tuberculosis has been shown to be so preëminently a disease of the home, it is but natural that the correction of housing conditions should have attracted the attention of the numerous workers in the crusade against this disease, almost to the exclusion of other possible errors in living.

In the prevention of this disease it must be appreciated that sufficient nutriment is equally as important as sufficient fresh air and rest, as has long been recognized in the treatment of the condi-

[1] Based on material collected by the Social Service Department of the Henry Phipps Institute, University of Pennsylvania, Philadelphia, under the Direction of Miss Lucinda Stringer.

tion. The treatment of the disease in a large measure consists in the carrying out of the methods of prevention to a greater degree than can usually be obtained in the ordinary case.

The predisposing factors which have received the greater share of attention have been the working and housing conditions of the people, the public having been instructed in the importance of fresh air and sufficient rest and warned against the danger of dissipation, all being dealt with in considerable detail. While attention has frequently been called to the importance of the proper food, in sufficient quantity and properly prepared, ignorance of the actual conditions existing has prevented the consideration of this subject in that degree of detail which its importance demands. Too frequently the entire subject is dismissed with a few vaguely general remarks.

One of the principal reasons why this subject has not received more attention undoubtedly lies in the fact that the food supply of a community is so extremely important and presents such a stupendous problem, involving such enormous economic factors, that its magnitude alone tends to discourage interference.

Method of Investigation. With the object of throwing some light upon the subject of nutrition, the Henry Phipps Institute in the early spring of 1915 started a study of the dietaries of twelve families. The study was continued during 1915 and the early part of 1916, the large majority of the cases being studied in the same season of the year.

As the season of the year appeared to exert no appreciable effect upon the cost of the food, it was considered possible to disregard the date of the investigation in the consideration of the results obtained.

Three families of each of the four races most frequently encountered in the dispensary of the Institute were selected for study, namely: Russian Jewish, Italian, Polish and Negro, only those families being chosen which it was believed would coöperate with the workers from the Institute in the carrying out of the study.

The general plan of the investigation was first carefully explained to the family and their consent to give all assistance possible was obtained. A detailed report of the various social conditions was

made out by the worker from the Social Service Department of the Institute, the entire field of work of the investigation being carried out by the regular staff of this department. Whatever value the present investigation may possess must be largely attributed to intelligent interest in the work displayed by the head of the Social Service of the Institute, Miss Lucinda Stringer, and the staff of nurses associated with her in that department, together with the care and patience employed in the collection of the necessary data.

A careful inventory of all food in the house was first obtained and a record made of its character, weight, and value, then for a fixed period, usually two weeks, although in a few instances longer, all food brought into the house was weighed daily and its character and cost recorded. At the conclusion of the period of investigation a second inventory was made similar to that made just before the study of the family was started. In this way it was possible to accurately determine the amount, character, and cost of the food consumed by the family during a definite period of time. It was unfortunately deemed impracticable to determine the amount of the food which was wasted, either by spoiling in preparation, by imperfect methods of preservation, or by ignorance of domestic economy.

The exact character, quantity, and cost having been determined, the caloric value of each separate article of food was computed from the tables of Atwater and Bryant.[1] The caloric value of each food represents its actual nutritive value, as allowance has been made for waste in the raw material and the available calories for each article have been carefully estimated in each particular instance. The calories used in the various studies which follow represent the actual nutritive value of the food as nearly as is possible in a study of this kind in which no analyses were made. The figures used must under the circumstances be considered approximate and not absolute.

The use of the caloric value of foodstuffs provides a convenient basis for comparing the results with those obtained in similar investigations. It will be noted that in the following tables the caloric value of the foods has been used exclusively, no reference

[1] The Chemical Composition of American Food Materials. U. S. Department of Agriculture, Bulletin No. 28, revised edition.

being made whatever to the weight of the various foodstuffs. This has been considered advisable, as it eliminates all confusion caused by the difference in value between the fats and proteins and carbohydrates. In computing the caloric value of the various foodstuffs the protein and carbohydrates have been reckoned on a basis of four calories to the gram, and fats on a basis of nine calories to the gram.

The study of a dietary cannot be confined to a study of the caloric value alone, there being other factors involved which affect the amount of actual nourishment derived from the food or influence the amount consumed. It is unfortunate that these factors are extremely difficult to estimate and even more difficult to express, and yet there can be no question that the flavor of the food, its digestibility, the selection of a proper variety, and the methods used for its preservation and preparation are quite as important as the actual caloric value of the food selected. It is not uncommon, however, to find reports based entirely upon the caloric value, the other factors being completely ignored.

In the present study the difficulty encountered in evolving a method of concisely expressing these factors in such a manner that the results might be compared with those obtained in similar studies has practically confined the study to the caloric value of the foods. The comparatively meager reference to the other factors must not be construed as in any way minimizing their importance.

A study of the food supply of a certain portion of the community must necessarily first take into consideration the estimation of the amount of nourishment ordinarily obtained, and the determination of whether this amount is sufficient for the proper nutrition of the individuals studied. If the amount is found to be insufficient the next step would naturally consist in an attempt to discover whether the lack of nourishment was due to the fact that the people were unable to purchase a sufficient quantity of food, or due to an improper selection of food materials through ignorance. If the first cause mentioned is correct economic factors are involved which are entirely outside the scope of the present study. If, on the other hand, the second is the reason for a food supply of insufficient caloric value there is the possibility that considerable improvement might be made in the dietaries of the poor by means of education.

The actual caloric requirements of an individual or group of individuals appears to be an extremely difficult matter to determine accurately, the number of calories required by the individual in the twenty-four hours varying with the authority consulted. It is only natural that this diversity of opinion should exist when one considers that one is dealing with organisms which vary greatly in their ability to digest, absorb and utilize the food consumed. Another factor of the greatest importance is that the necessary intake of food is chiefly determined by the amount of movement and the extent of physical labor undertaken by the individual. The differences due to size and weight, age and sex, being more important from a theoretical than from a practical viewpoint.

The difficulty in determining the amount of labor actually performed by the individuals in a study like the present renders the estimation of what constitutes sufficient nourishment so extremely perplexing. For convenience the rather arbitrary standard of Atwater has been adopted in the present investigation.[1]

The total number of "men" in each family being estimated according to Atwater's scheme. Thus a family consisting of a man at hard muscular work (1.2), a woman at moderately active work (0.8), a boy of twelve years (0.7), and a girl of ten (0.6) would be reckoned as a family of 3.3 "men." If a family like that just mentioned was found to have a dietary which provided 9900 available calories daily the family would be considered as having a dietary of 3000 calories per man per day. This method of estimation is described in detail to avoid any possible confusion in regard to either the actual number of individuals in the family or the number of calories which each member of the family received daily.

Total Caloric Value of Dietaries Studied. The first point to be determined is whether the families are receiving the number of calories per "man" per day that they require for their proper nutrition. The condition found in the twelve families studied are given below, the families being designated by the small letters, a, b, c, etc., the capital letters indicating the race: I for Italian, J for Russian Jewish, P for Polish, and N for negro, these letters being used for the same families throughout the entire study.

[1] Principles of Nutrition and Nutritive Value of Food, U. S. Department of Agriculture, Farmers' Bulletin No. 142, page 33.

TABLE I.—NUMBER OF CALORIES CONSUMED PER "MAN" PER DAY BY EACH FAMILY IN COMPARISON TO THE AMOUNT REQUIRED (3400)

Family.	Number of men (computed).	Calories per man per day consumed.	Caloric deficit per man per day.	Caloric excess per man per day.
I. a.	4.3	2877.0	523.0	
I. b.	7.6	2589.0	811.0	
I. c.	2.6	2605.0	795.0	
J. d.	2.4	3279.0	121.0	
J. e.	2.5	2118.0	1282.0	
J. f.	2.3	2521.0	879.0	
P. g.	2.4	2975.0	425.0	
P. h.	3.2	2997.0	403.0	
P. j.	2.9	3399.0	1.0	
N. k.	4.2	2774.0	626.0	
N. l.	3.7	2370.0	1030.0	
N. m.	2.5	3697.0	..	297.0
Total	40.6	34201.0	6896.0	297.0
Average	3.38	2850.0	549.0	

The above table shows that only one family (N. m.) out of the twelve studied was receiving more calories per man per day than the actual requirement according to Atwater, who gives 3400 calories as the requirement of a man per day. The explanation of why this one family should be receiving such a relatively high caloric dietary is probably to be found in a study of the dietary in detail, the family consuming about 300 grams of lard daily. One other family (P. j.) received practically the amount of nutrition required (3399 calories), but this family paid more for their food than any of the families studied, their food costing them $0.4118 per man per day. The ten families remaining show a deficiency in the number of calories per man per day ranging from 121 to 1282 calories, with an average deficiency of 689.5 calories per man per day. This means that ten of the twelve families studied (83 per cent.) were only receiving on an average about 80 per cent. as much food as they actually required.

The standard daily requirement for a man at moderate exercise is given by Voit as 2965 calories, which is distinctly lower than the 3400 calories as given by Atwater. When the families were studied according to Voit's figures it was found that five were receiving more than the amount required, averaging 304 calories in excess, and seven families were receiving less than the required amount, an average deficit of 414 calories. According to Voit's figures,

therefore, 58.3 per cent. of the families studied were receiving only 86.1 per cent. of the required amount of nourishment.

The average deficit for the entire twelve families was 549.9 according to Atwater's figures, a deficit of approximately 16 per cent. According to Voit's figures the average deficit for the twelve families was 114.9, a deficit of 3.8 per cent.

The results based upon Atwater's figures represent more accurately the actual conditions existing. It does not seem rational to compare conditions in this country to a European standard as represented by Voit's figure.

The average number of calories per man per day in the study of these twelve families was found to be 2859 calories, a figure remarkably near the figures given by Atwater from a study of the diet of twelve laborers' families in large cities of the United States, namely, 2810, and of eleven poor families in New York City, 2845. The findings in the present study may be considered typical of the families of their class, and probably could be duplicated in almost any large city in this country.

The figures showing the lack of nutrition in the families studied merely demonstrates, in a graphic manner, what one would expect to find in studying the dietaries of the average dispensary patients. It is not surprising that ten of the twelve families studied were not receiving sufficient nutriment, but that two of them should be receiving sufficient. The reasons for these two cases receiving the large number of calories have already been given.

The families were of four races, with their peculiar customs, habits, and characteristics, and these are probably manifested to a marked degree in their selection, preparation, and purchasing of food materials. While the number of families of each race studied is too small to warrant the drawing of any very definite conclusions, the findings are at least very suggestive.

TABLE II.—AMOUNT OF NOURISHMENT AND COST ACCORDING TO RACE

Race.	Average calories per man per day for race.	Average cost per man per day for race.
Italian	2690	$0.1910
Russian Jewish	2639	.2409
Polish	3123	.3469
Negro	2947	.2215

The race receiving the largest average number of calories per man per day was the Polish, the next highest being the negro, and the Italians and Russian Jews receiving approximately the same amount. The most striking feature of the chart is found in the amounts that the different races paid per man per day for their food. The Poles received the largest number of calories and paid the most for them, the Russian Jews received the lowest number of calories and paid next to the highest for them, the Italians paying the least for their food. This point is merely referred to in passing, as this question is considered in more detail in a subsequent section dealing with the selection and purchase of food.

The fact having been established that in the families studied there existed a deficiency in the amount of nutriment, the more difficult problem presents itself of determining the cause of this lack of nourishment, whether due to poverty or ignorance. In attacking this problem the first point to be determined is whether there exists any relation between the number of calories obtained per man per day and the amount paid for the food per man per day.

The cost of food per man per day was based upon the total amount of money spent upon food during the investigation, in this sum being included the amounts spent upon condiments and beverages, such as salt, pepper, tea, coffee, etc., which did not possess any caloric value.

It was believed that if there was found to exist a definite fixed relation between the number of calories per man per day and the cost of the food per man per day, one would be justified in believing that the amount of nutriment obtained was dependent entirely upon the financial resources of the family.

In order to determine this point the families were placed in order of the number of calories obtained per man per day and the corresponding cost of food per man per day was placed opposite.

It will be seen that when the individual families are studied the relationship between calories and cost is not an absolute one. For a more general study the families were divided into four groups of three families each and the average calories and cost for each group was placed in a separate column. A study of these averages shows that the relation between calories is closer than when individual

families are studied, but even here it is not absolute, as the third and fourth groups showed absolutely the same average cost while there was a difference in the average calories of slightly over 300.

TABLE III.—SHOWING RELATION BETWEEN THE CALORIES AND COST PER MAN PER DAY

Family.	Calories per man per day.	Cost per man per day including condiments and beverages.	Average calories per man per day.	Average cost per man per day.
N. m.	3697	$0.2496		
P. j.	3399	.4118	3458	$0.3218
J. d.	3279	.3041		
P. h.	2997	.3080		
P. g.	2975	.3210	2949	.2623
I. a.	2877	.1580		
N. k.	2774	.2100		
I. c.	2605	.1870	2656	.2086
I. b.	2589	.2290		
J. f.	2521	.1950		
N. l.	2370	.2070	2336	.2086
J. e.	2118	.2238		

If this relation between calories and cost was an absolute, fixed relationship the same results should be obtained by arranging the families according to the cost instead of according to calories as in the preceding table. When arranged in this manner the averages for the groups were not even as constant as in the preceding table.

One would be justified in concluding from the above that while the amount spent for food influenced the number of calories obtained to a certain extent, the number of calories obtained was not entirely dependent upon the amount spent. There appears to be some other factor involved which affects the relation between cost and calories. The only factor which could affect the result would be the nature of the food selected—in other words, the possibility of certain families obtaining more nourishment for the amount expended.

The only method which suggests itself for determining the ability of a family to select food with a high caloric value for the least amount of money is by comparing the number of calories obtained by each family for ten cents, a sum used as a standard by other writers on this subject.

The amount of nutriment obtained for ten cents varied greatly in the different families, the number of calories ranging between 884 and 1813, with an average of 1178. The question of racial

influence, with its accompanying habits and customs, upon the selection of food is always extremely interesting. It will be seen that the Italians are the best purchasers, obtaining the greatest number of calories for the same sum of money. The Negroes were next to the Italians in this regard, and the Poles were the poorest purchasers of the races investigated in the present study.

TABLE IV.—SHOWING NUMBER OF CALORIES OBTAINED FOR TEN CENTS BY EACH FAMILY AND EACH RACE

Family.	Calories for $0.10 (including condiments and beverages).	Average calories for $0.10 for race.
I. a.	1813	
I. b.	1127	1443.1
I. c.	1389	
J. d.	1078	
J. e.	946	1104.9
J. f.	1290	
P. g.	926	
P. h.	970	927.2
P. j.	884	
N. k.	1317	
N. l.	1122	1238.5
N. m.	1276	
Average	1178	

The reasons why the Poles receive so little for their money, in spite of the fact that they spend the most for their food as shown by Table II, and why the Italians receive so much, can only be determined by a study of the dietaries in detail. It would appear from the study so far as if the negroes had the most evenly adjusted dietary, being second in the number of calories obtained per man per day and second in the number of calories obtained for ten cents.

The most important point to be determined is whether there exists any relation between the number of calories obtained for a certain sum and the cost of food per man per day. If this relation is found to exist, whether it is more definite and constant than the relation between the number of calories obtained per man per day and the cost of food per man per day. In other words, whether the purchasing or selecting ability influences the amount of nourishment obtained by the family to a greater extent than the amount actually expended.

In order to determine this point the families have been graded according to the number of calories obtained for ten cents, with the

corresponding amount paid per man per day for food in the second column. For greater simplification the families have been grouped in series of three with the average for each group.

TABLE V.—SHOWING RELATION BETWEEN THE NUMBER OF CALORIES OBTAINED FOR TEN CENTS AND THE COST OF FOOD PER MAN PER DAY

Family.	Calories obtained for ten cents.	Cost per man per day.	Average calories obtained for $0.10.	Average cost per man per day.
I. a.	1813	$0.1580		
I. c.	1389	.1870	1506	$0.1850
N. k.	1317	.2100		
J. f.	1290	.1950		
N. m.	1276	.2496	1231	.2245
I. b.	1127	.2290		
N. l.	1122	.2050		
J. d.	1078	.5041	1056	.2723
P. h.	970	.3080		
J. e.	946	.2238		
P. g.	926	.3210	918	.3188
P. j.	884	.4118		

The foregoing table is extremely interesting because it shows that not only a definite inverse ratio exists between the number of calories obtained for ten cents and the cost of food per man per day in the average for each group, but that this also holds true of the individual families with but few exceptions.

If this relationship is exact, or approximately exact, the same results should be obtained if the families are graded according to the cost of food per man per day, and in the same manner as in the preceding table.

Graded according to the cost of food per man per day, this inverse ratio, while not as definite as in the preceding table, was found to be more exact than in those tables showing the relation between the number of calories obtained per man per day and the cost of food per man per day. In other words, the purchasing ability of the family seems to exert a more definite effect upon the amount expended for food than the amount expended for food does upon the number of calories obtained. This would indicate that the amount the family spent for food was influenced by or dependent upon the purchasing ability of the family to a much greater extent than the amount of nourishment obtained is influenced by the amount of money expended for food. One would appear justified

in concluding that ignorance of the nutrient value of food was mainly responsible for the lack of nutrition, although poverty was responsible to a certain extent.

The greatest number of calories obtained for ten cents was 1813, by Family I. a. If every family studied had possessed this family's ability to select food possessing a high nutritive value for a low price, what would be the amount of nutriment obtained, supposing they continued to expend the same amount of money as before? If we take the amount of money spent daily by each family per man and note the number of calories it would provide, if they were able to obtain 1813 calories for ten cents as family I. a. was able to do, only two families would receive less than 3400 calories required and the twelve families would average 1135.9 calories more than the 3400 calories per man per day required.

The 1834 calories for ten cents was so much in excess of that obtained by any other family that this comparison seems hardly fair, and yet it shows what can be done by careful judicious purchasing and selecting of food materials. Taking the average amount expended for food $0.2502, and estimating how many calories must be obtained for ten cents to provide the 3400 necessary calories, one finds that approximately 1359 calories would have to be obtained. This number of calories for ten cents was exceeded by two families (I. a and I. c.) in the series investigated. It would seem, therefore, that 83 per cent. of the families studied were not obtaining the nutriment they should for the amount expended, and the amount they could obtain if properly instructed.

The need of educating the poor in the necessity of selecting foods of high nutritive value at a low cost appears to have been conclusively demonstrated. The possibility of obtaining food with sufficient nutriment for a slight cost has also been demonstrated by the experience of two of the families studied. The ways and means of carrying out this crusade of education presents a problem of such a wide scope that it appears impossible to attempt to even sketch it in outline in a paper of this kind. It does seem, however, that the school-houses, as community centers, might be utilized in the large cities in the carrying out of a scheme which might reach the poorer classes in sufficient numbers to warrant the expense.

In a scheme of this kind the nurse with training in public health work would be specially valuable. The necessary knowledge of food economics and dietetics together with a broad knowledge of general hygiene in the home would make them peculiarly fitted for carrying out this sort of work.

There is another factor to be considered in studying the cost of food per man per day, and that is the number of men composing the family.

The size of the family to be catered for appeared to affect the cost of the food—the larger the family, the lower the cost of food per man per day up to a family of less than four "men." In families of four "men" and over the size of the family did not seem to exert the same effect upon the cost.

The Relative Proportion of Protein, Fat, and Carbohydrate in the Dietaries Studied. In expressing the proportion of the various food constituents it was deemed advisable to reduce them all to the common factor of "available calories." For this reason it is impossible to compare the proportions or gross figures with those obtained in similar investigations in which the proportion and amounts represent grams and not calories.

Table VI.—Proportions of Food Constituents

Family.	Total calories per man per day.	Percentage protein calories.	Percentage fat calories.	Percentage carbohydrate calories.
I. a.	2877	11.6	18.5	69.8
I. b.	2589	13.7	20.8	65.4
I. c.	2605	7.7	19.3	72.9
J. d.	3279	12.4	32.0	55.5
J. e.	2118	14.8	25.8	59.3
J. f.	2521	13.1	24.9	61.9
P. g.	2975	12.4	25.6	61.9
P. h.	2997	14.1	28.8	57.1
P. j.	3399	15.0	37.3	47.6
N. k.	2774	12.5	37.0	50.4
N. l.	2370	11.1	31.2	57.6
N. m.	3697	9.6	55.4	34.9
Average	2851	12.3	30.8	56.8

The most striking feature in the preceding table is the almost constant relation between the proportions of the various constituents in each family studied. In every instance the smallest proportion of calories is derived from protein, the next highest from fat, and in every instance but one the largest proportion is derived

from carbohydrate. This one exception (Family N. m.) showed a greater proportion of fats than carbohydrates, due to the large amount of lard used, a fact which has been previously mentioned.

A comparison of the average proportions of the various constituents with the average of several investigations, cited by Atwater, among families of the same station in life as those under consideration shows that the two correspond to a remarkable degree. The percentage of protein calories was 12.3 in one series and 13.5 in the other, of fats 30.8 in one and 31.1 in the other, and carbohydrates 56.8 in one and 55.4 in the other.

It would therefore seem that no matter what variations might exist in the diets of individual families both in quantity and character of the food, similar groups of families show a remarkably constant proportion of the calories derived from the various constituents. The variation in the total number of calories obtained is very much greater than in the proportions of protein, fat, and carbohydrate.

TABLE VII.—FOOD CONSTITUENTS ACCORDING TO RACE

Race.	Total calories.	Protein calories per man per day.	Proportion of protein calories. Per cent.	Proportion of fat calories. Per cent.	Proportion of carbohydrate calories Per cent.	Cost of food per man per day.
Italian . .	2690	297.2	11.0	19.5	69.4	$0.1910
Jewish . .	2639	350.6	13.3	27.6	59.0	.2409
Polish . .	3123	432.8	13.8	30.6	55.5	.3469
Negro . .	2947	322.7	10.9	41.3	47.7	.2215

A comparison of the average composition of the food for each race shows that one of the chief differences between the dietaries consists in the variation in the relative proportion of fat and carbohydrate, the proportion of protein calories showing only a slight variation. It may be worth noting, however, that there was a constant relation between the number of protein calories and the cost of food per man per day.

In the Italian families the proportion of fats consumed was the lowest and the carbohydrates the highest of the races studied. The negroes gave the highest proportion of fats and the lowest carbohydrate, the other two races being almost midway between the Italians and negroes.

In other investigations of a similar character the greatest variation appears to have been between the proportions of protein and fat, the carbohydrates remaining fairly constant. The only explanation for the existing conditions may be found in the large quantity of fat in the form of lard consumed by one of the negro families (N. m.) In the figures cited by Atwater giving the proportions of the various food constituents found among the Italians, Russian Jews and negroes, the negroes showed the largest proportion of fats and the Russian Jews the highest percentage of protein, just as was found in the present study although to a greater extent. In both studies the negroes showed the lowest percentage of protein.

It seems rather remarkable that among civilized races, living under similar climatic conditions, in the food selected by the people in the poorer classes the proportion of the various constituents should so closely approximate one another. It would appear as though food requirements of the body had been gradually determined by experience and became standardized in course of time. No matter how the diet varies in its articles of food and method of preparation the relation of the various food elements remains remarkably constant. It might be urged that this may be due to the fact that the investigations were carried out in the same country. Three of the races studied were from foreign countries, living in a large city and to a great degree associating with their fellow countrymen, a condition which tends to maintain their natural customs and habits. The markets from which their food is selected is practically unlimited as far as variety is concerned. It can hardly be said that in the large cities of the United States the diet of any group of people could be influenced to any marked degree by the limitations of the market or influenced by the example of their new associates.

The proportion of protein found in the present investigation is distinctly lower than the standard or physiological proportion as given by Atwater and by Voit, 12.3 per cent. as compared to 14.8 per cent. and 16.1 per cent. Atwater does not give the proportion of fat and carbohydrates, but Voit gives a percentage for fat (16.8) which is approximately one-half the proportion encountered in the present study (31.1 per cent.), the carbohydrate percentage being accordingly much higher in Voit's standard figures.

It was thought that perhaps it might prove of interest to study the relation between the total protein calories per man per day and the cost of food per man per day (Table VIII). Charts were also prepared showing the relation between the cost of food per man per day and the percentage of protein, fat, and carbohydrate, the families being graded according to the amount or proportion of the various food elements and then divided into groups of three for greater convenience, with the average for each group.

TABLE VIII.—SHOWING RELATION BETWEEN PROTEIN CALORIES PER MAN PER DAY AND THE COST OF FOOD PER MAN PER DAY

Family.	Protein calories per man per day.	Cost of food per man per day.	Average protein calories.	Average cost.
P. j.	510.0	$0.4118		
P. h.	420.1	.3080	445.5	$0.3413
J. d.	406.4	.3041		
P. g.	368.3	.3210		
N. m.	356.3	.2496	359.9	.2665
I. b.	355.3	.2290		
N. k.	349.2	.2100		
I. a.	334.3	.1580	338.2	.1876
J. f.	331.3	.1950		
J. e.	314.3	.2238		
N. l.	262.8	.1850	259.7	.1986
I. c.	202.1	.1870		

There exists an apparent relationship between the number of protein calories per man per day and the cost of food per man per day, but this relationship is not so evident or constant as one might expect to find. The first group having the highest average number of calories shows the highest average cost, and the group with the second highest average calories the second highest cost. The group with the third highest average calories, however, shows an average cost lower than the group with the fourth highest average calories.

As will be seen later the protein is the most expensive of the food elements, and one would naturally expect to find it exerting a more constant or at least a more evident influence upon the cost of food. The influence of the protein upon the cost is seen when the families are studied according to the race, mention of which has been previously made (note under Table VII). When the families were grouped according to the race and the average for each race obtained the relationship between the protein calories and cost of food per man per day was found to be absolutely constant. The Poles

showed the highest number of protein calories and the highest cost per man per day. The Russian Jews showed the second highest of each, the negroes third highest, and the Italians the lowest calories and cost.

It seems hardly justifiable to use the total protein calories as a factor in studying the relation between protein and cost, the total protein calories being influenced to such a marked degree by the total amount of food obtained. It would be much more correct to use the proportion of protein in such a comparison rather than the total amount of protein.

The relation between the proportion of protein and the cost was not found to be any more constant than the relation between the total protein calories and the cost, although this latter finding would certainly seem to have more significance than the former. One would naturally expect that the proportion of the most expensive food element would bear a fixed relationship to the cost of food.

The proportion of fat did bear a constant relation to the cost of food, the greater the proportion of fat the higher the cost, the increase in cost, however, not being proportionate to the increase in percentage of fat.

When the relation between the proportion of carbohydrate and cost was studied the relation was found to be not only a constant one but there was almost an absolute inverse ratio between the two, the cost of food decreasing proportionately with the increase in the percentage of carbohydrate. The relationship was so marked and so proportionate that it would appear as if the carbohydrate must be considered the most important element of the food in the maintaining or securing of an economical dietary.

In referring to protein, fat, and carbohydrate it must be remembered that in the present study the various elements have been considered separately regardless of the source of the element. For example, the protein referred to was considered as a whole, although it was derived from vegetables, legumes, dairy products, and meats. The source of the protein is, however, of considerable importance from an economic stand-point. This is the only possible explanation of the failure to note a more constant relation between the percentage of protein and the cost of food.

In the original tables each article of diet was considered separately, with the percentage of calories derived from proteins, fat, and carbohydrate given in full. The cost of the food was divided in the same proportions and assigned to protein, fat, and carbohydrate. For example, if twenty cents was spent for a certain article of diet containing 25 per cent. protein calories, 25 per cent. fat calories, and 50 per cent. carbohydrate calories the sum of five cents was credited to protein, five cents to fat, and ten cents to carbohydrate. In this way the actual cost of each food element was accurately obtained, it being then possible to determine the proportionate cost of each food element for each family.

TABLE IX.—SHOWING PROPORTIONATE COST OF PROTEIN, FAT CARBOHYDRATE

	Protein. Per cent.	Fat. Per cent.	Carbohydrate. Per cent.
Average percentage of calories	12.3	29.7	57.8
Average percentage of cost	20.2	37.4	42.3

	Protein.	Fat.	Carbohydrate.	Total.
Average calories per man per day	350.8	879.4	1620.9	2851
Average cost per man per day	$0.052	$0.094	$0.104	$0.2501

AVERAGE CALORIES FOR TEN CENTS

	Protein.	Fat.	Carbohydrate.
	674	935	1558
Ratio	1	1.4	2.3

AVERAGE COST OF 1000 CALORIES

	Protein.	Fat.	Carbohydrate.
	$0.148	$0.107	$0.064
Ratio	1	.70	.43

If the various food constituents are reduced to a common basis of the average cost of 1000 calories it will be seen that the protein was nearly two and a half times as expensive as the carbohydrates and almost half again as expensive as the fats, the fats being approximately one and two-thirds as expensive as the carbohydrates. It is very interesting to see the actual amount spent on the average for each man daily for protein, fat, and carbohydrate.

If the average number of calories had been derived from carbohydrate alone, at the relative cost for carbohydrate as given, the average daily cost of food per man would have been reduced from $0.2501 to $0.1825, or if derived from protein alone in the same

manner it would have been increased to $0.4219. This must not be taken as a recommendation, but is merely stated to bring out more clearly the difference in cost of these two elements.

The protein is derived from various sources, and it was therefore thought it might prove of interest to see what the difference in cost would be according to the foodstuffs from which it was derived.

TABLE X.—NUMBER OF PROTEIN CALORIES OBTAINED FOR TEN CENTS (AVERAGE OF TWELVE FAMILIES)

		Ratio.
When derived from eggs, meats and fish	448	1.0
When derived from vegetables, legumes, fruits, dairy products, and mixed foods	1264	2.8

It was found that the total number of calories obtained from vegetables, legumes, fruits, dairy products, and mixed foods in the dietaries studied was 1.69 times that obtained from eggs, meat, and fish. It will be noted that the protein derived from eggs, meat, and fish is two and eight-tenth times as expensive as that obtained from the other sources.

STUDY OF THE DIETARIES IN DETAIL. The attempt was made to so arrange the dietaries that a comparison could be made between the different families. For this purpose a chart was made out for each family by which it was possible to determine which were the articles of food which were bought most cheaply and which were the expensive foods in the case of each family. When, however, an attempt was made to correlate these tables the number of the articles of food was so great that they did not lend themselves readily to comparative tables.

It was therefore deemed advisable to merely select from the dietary of each family the twelve or thirteen articles of diet from which the greatest number of calories was obtained, in other words, their main articles of diet. The number of calories obtained from each article was noted and for each family the approximate percentage of that article consumed was placed opposite.

The most striking feature of the charts thus prepared was the relatively large amount of bread consumed by every family. When the wheat bread, wheat rolls, and rye bread were combined it was seen that they constituted on an average 33 per cent. of the twelve

main articles of diet. This average would have been much higher if one of the families (N. m.) had been omitted, five families giving a percentage of over 40.

One would naturally expect that the amount of meat and eggs consumed would affect to a great extent the cost of the food, as shown by the number of calories obtained for ten cents. While in a general way it can be said that the families with the larger proportions of meat were among those obtaining the fewer calories for ten cents, the relation was not an absolute one.

A study of the above dietaries would seem to show that within certain limits it was not so much the articles of food purchased which influenced the economy of the diet as much as it was the purchasing ability of the housewife. For example, when one studied the various articles of diet when purchased by different families one was struck with the distinct variation in the amount of nutriment obtained for the same amount of money. For example, wheat bread constituted a portion of the dietary of every family, the number of calories obtained for ten cents ranging between 1920 and 3901. This marked variation is probably due to the amount of stale bread used by the different families and also to the kind of bread used.

The variations in the amount of nutriment obtained for ten cents in the other articles of diet may probably be attributed to the differences in quality or grade, and the normal fluctuations in market price.

Summary. From the study of the twelve families investigated one would seem justified in drawing the following conclusions:

The average dispensary family obtains about four-fifths of the nourishment it should receive.

Ignorance of the nutrient value of food and poor judgment in its purchase is the main cause of this state of affairs, although poverty is to a certain extent also responsible.

Education of the poorer classes in dietetics and food economy would undoubtedly, if made sufficiently wide-reaching, lead to a marked improvement in their nutrition and general well-being.

THE ETIOLOGY OF PELLAGRA: A CONSIDERATION OF VITAMIN DEFICIENCY

By EDWARD J. WOOD, M.D.
WILMINGTON, NORTH CAROLINA

In a previous communication[1] it was suggested that the relation of corn to pellagra was analogous to the relation of rice to beriberi. The object of the present study was to determine the results of feeding chickens and pigeons on the offal of the corn mill (which is known as corn chops) after the development of symptoms produced by feeding deficient corn products. The second portion of the work has to do with the application of the information obtained by animal experimentation in the treatment of pellagra in man. Soon after starting the present work it became apparent that the milling and cooking of wheat products played an equally important part in the production of vitamin deficiency.

It had been shown by John M. Little[2] that deficient wheat flour caused a form of polyneuritis in man which must be counted true beriberi. W. R. Ohler,[3] prompted by a suggestion from Little, did extensive experimentation and produced the same type of polyneuritis by feeding chickens hominy as had been produced by deficient wheat. The result in both instances was the same as the type of polyneuritis produced with polished rice.

In 1914 Casimir Funk,[4] who had introduced into medicine the term vitamin, and who had seen his theory regarding the causation

[1] Wood, E. J., Vitamin Solution of the Pellagra Problem. Jour. Am. Med. Assn., May 16, 1916, vol. lxvi.
[2] Jour. Am. Med. Assn., 1912, lviii, and 1914, lxiii.
[3] Jour. Med. Research, vol. xxxi (new series, vol. xxvi).
[4] Prophylaxe u. Therapie der Pellagra im Lichte der Vitaminlehre, Munchen. med. Wchnschr., 1914.

of beriberi and its remedy verified, suggested that there was the same relationship between the milling of corn and pellagra as had been proved between the milling of rice and beriberi. There was no experimental or clinical evidence presented, however, and the suggestion did not receive the attention it deserved, though the advocates of a deficiency cause never lost sight of the possibility of such a solution. Funk pointed out the marked difference in the composition of corn and of the germ of corn. The fat content of the whole grain is 5 per cent., while the germ contains 30 per cent. The loss of fat was thought by him to be a good indicator of the loss of vitamin, as there was evidence to show that the fatty portion contained the vitamin. South African and American corn were both deficient, but the latter more so because of the higher degree of milling. Funk was disposed to regard the mortality rate of the disease as an index of the degree of deficiency.

It had been shown in the beriberi work that phosphorus pentoxide was a reliable indicator of vitamin, though there was no direct connection between the two. The same value is attached to it in the present work. Sulphur determination is being introduced by us as an aid in determining vitamin, but the work has not progressed far enough to justify any definite conclusions as to its value in comparison with the phosphorus indicator. So far the results obtained show a striking similarity.

Viewing pellagra as a deficiency disease, and attributing the deficiency to the milling process or to some chemical change which brings about destruction of vitamin in the process of cooking, it is no difficult matter to reconcile and even harmonize many of the views of the early Spanish, Italian, and French pellagrologers. The vast amount of literature which has accumulated since the publication of Casal's[1] original article has been very lifeless until recently. It now becomes reanimated by recent progress, and a careful study of this wealth of material is not only interesting, but of practical value, and we are filled with admiration at the keenness of the observation of those men who had so little oppor-

[1] Historia natural y medica de el Principado de Asturias. Abra posthuma del Doctor D. G. Casal, Medico de Su Magestad y su Protomedicin de Castilla, Madrid, 1762.

tunity for the accurate study of such a problem, and whose observations have stood so well the test of modern scientific advance. Sandwith[1] states that as early as 1707 Pedro Casal wrote in Spanish that pellagra was due to insufficiency of diet. In the latter part of the eighteenth century Franzago declared that maize was unhealthy only because it was an insufficient food, but he would not say it was the sole cause. Later Marzari[2] claimed that the cause of the noxiousness of the corn was an insufficiency of gluten. Had there been a knowledge of Funk's theory of vitamin during that period in which corn was connected with pellagra in one way or another, the problem would probably have been solved long ago. The school of Lobroso had as a basis of its teachings a definite toxicity which may now be interpreted in terms of deficiency.

The germ of the corn lying at the hilus of the grain is poorly protected and subjected to the action of all injurious agencies, both animal and vegetable. Damaged corn is always most affected in this part. Owing to the high fat content, the method of removing the germ before the grain was finally ground was introduced. This process was called "degermination." It is practised in many places and in many types of mill.[3] The two products of this form of milling are granulated cornmeal and corn chops. The latter is spoken of as the offal of the corn mill and is sold as cattle food. In former times the grain was ground whole at the community water mill, and there was no damage from the great heat which may be produced in rapid steam milling. This form of heat, however, is inconspicuous in comparison with the heating process which the grain often undergoes before reaching the mill.

The differences between corn chops and cornmeal are given below:

	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Fiber. per cent.
Meal	9.2	1.9	74.4	1.0
Chops	9.0	7.0	70.0	9.0
Germ alone	21.7	29.6	44.7	
Endosperm	12.2	1.5	85.0	

Analysis of the various articles of food which were experimented with showed interesting variations in the P_2O_5 content. It was

[1] Trans. Soc. Trop. Med. and Hyg., October, 1915.
[2] Essai Medico-politique, 1810.
[3] Farmer's Bulletin, No. 298, U. S. Dept. Agr.

readily apparent that the cortex of the various grains, as has been formerly held, contained the bulk of phosphoric acid. It was also apparent that the amount was influenced by the degree of fineness of the product. Wheat middlings sifted in the laboratory with the removal of only the very smallest amount of bran showed a definite decrease in the phosphorus.

	P_2O_5 per cent.
Corn chops	1.15
Water-ground meal (North Carolina)	0.78
Whole meal, steam milled (Virginia)	0.60
Highly milled meal (Ohio)	0.29
Steam-milled meal (North Carolina)	0.58
Wheat middlings (offal of mill)	0.98
Whole-wheat flour	0.50
Average wheat flour (bought in Wilmington, North Carolina)	0.14

The first important suggestion of a vitamin deficiency caused by the milling process was made by P. A. Nightingale[1] in Rhodesia in 1912. He found that prisoners fed on highly milled meal developed a definite group of symptoms for which he coined the word "zeism," thinking it to be a new condition. There can be no doubt that this condition was acute pellagra, which has never been reported in medical literature except in the Southern States, where it appeared in 1905. All references in European literature recognize pellagra only as a chronic process. Nightingale concluded that the use of highly milled meal had caused the disease, and substituted whole meal which was ground by hand in the jail. The result in his words was "immediate and magical."

Recent studies in polyneuritis gallinarum in its relation to beriberi now become of great value in suggesting a line of investigation in pellagra. Goldberger[2] has emphasized the importance of viewing pellagra in much the same light as beriberi, and we are indebted to him for the suggestion. It is not known that there is any connection between pellagra and beriberi, except that both diseases are probably deficiencies. Any experimental work in pellagra would therefore not be aided by a study of polyneuritis in fowl. The present work was undertaken to prove the fact that polyneuritis could be caused

[1] Nightingale, P. A., Transvaal Med. Jour., 1912.

[2] Public Health Reports, June 24, September 11, October 23, 1914, Jour. Am. Med. Assn., October 10, 1914, and February 12, 1916, Public Health Reports, January 15, 1915.

by meal made deficient in the milling process and cured by the portion of the grain removed in the production of the deficiency. Unexpected findings have thrown considerable light on the question, and have tended to suggest the possibility of a disease condition which seems to be due to a deficiency not so marked as to be sufficient to cause polyneuritis. It would seem that beriberi and pellagra, then, differ only in the degree of insufficiency.

The recent work of Voegtlin, Myers, and Sullivan[1] showed that vitamin was promptly destroyed by the use of soda and certain baking powders in the preparation of bread regardless of the original quality of the flour or meal. It was further shown that this could be prevented by the use of sour milk in conjunction with the alkali. Some baking powders contain enough tartaric acid to neutralize the sodium carbonate after the liberation of carbon dioxide. It is an interesting study to trace the introduction of this form of cooking and the appearance of pellagra, just as it is interesting to study the time connection between the introduction of highly milled meal and the disappearance of the old water mill which ground the corn *in toto*. In one community, at least, I have been able to show that the year which marked the abandonment of the old mill was the year of the appearance of the first cases of pellagra. Pellagra was unknown in the Confederate Army, though lack of food was frequent; but there was no deprivation of the grains of any portion in the milling. There are broad areas in North Carolina where pellagra has never occurred, though poverty and poor hygiene obtain in the fullest. These areas are separated from railroad travel, and home products are used through necessity. This is particularly true of the remote mountain counties. I have searched diligently through four such counties and have never been able to find the disease, nor could I learn of its occurrence from the physicians. But as the Piedmont section is reached and the people are able to procure manufactured products of every sort, the disease soon appears and reaches its high point in the cotton-mill village, where highly milled products are used almost exclusively, and soda is added to every form of food to hasten the cooking (Voegtlin, Myers, and Sullivan).

[1] Voegtlin, Myers, and Sullivan, Public Health Reports, April 14, 1916.

Six pigeons were placed in a roomy cage outdoors with a floor to prevent the scratching of the earth. The best pigeon grit was abundantly supplied as well as plenty of fresh water. Whole corn was broken in the laboratory and allowed in great abundance. No other food was given throughout the experiment. For four months there were no developments of disease, though it was evident that conditions were not best suited for growth and development. At one time it was noted that there was some droopiness, and investigation showed that the corn used at the time was of an inferior quality. From that time seed corn was used. This group were the controls.

In the second group of pigeons the food was cornmeal with a P_2O_5 content of 0.58 per cent. After ten days it was noted that the pigeons had red legs, in striking contrast to the controls, though of the same breed and age. In addition to the red legs there was marked droopiness and inactivity. After six weeks a more deficient meal with a P_2O_5 content of 0.29 per cent. was substituted. There was no change except increased redness of the legs. After these twelve weeks there had occurred only one death, and that from a cause having no bearing on the experiment. At this time it was decided to produce polyneuritis gallinarum if possible. Wellman and Bass,[1] as well as Ohler, had produced polyneuritis in less than three weeks on a diet better than the one in use by us. The most deficient meal was made into bread, with the addition of soda. After a month of this feeding there was still no polyneuritis. During the experiment two squabs had been hatched from eggs laid after the experiment had been several weeks under way. These squabs did very well until the time for them to feed themselves. In a very few days polyneuritis developed. By the administration of corn chops there was prompt relief. It is a notable fact that these young pigeons were the only victims of polyneuritis, though the diet was such that it was to be expected that none of the animals would escape. The successful feeding of corn chops proved for corn what had already been proven for rice and wheat. By alcoholic extraction, a substance was found in the corn chops which was equally as effec-

[1] Wellman and Bass, Am. Jour. of Trop. Dis. and Prev. Med., 1913.

tive as the alcoholic extract of rice polishings had been in former experiments.

It appeared that continued feeding of a gradually increasing deficiency diet resulted in the acquiring of a peculiar kind of tolerance which may later be shown to explain some of the peculiarities of pellagra. After red-legged pigeons had been kept on the same food for several weeks it was impossible to produce polyneuritis with the most deficient diet, and the red-legged condition was just as promptly relieved by feeding corn chops as was polyneuritis. Only a few days were required for a return to normal, though it was found that the longer the red-legged condition had existed the longer the time required for a complete subsidence.

Chickens hatched on the same day were divided into two groups. One group was fed deficient cornmeal while the control group was fed corn chops. The food of the deficiency group contained 0.58 per cent. P_2O_5 in the beginning, which was later replaced by a meal with a 0.29 percentage. The red-legged condition did not occur, but the chickens did poorly. There was one case of polyneuritis gallinarum which did not respond to treatment because discovered late. The growth in every case was below normal and droopiness was quite marked. At the end of the experiment the chickens fed on corn had gained 8 per cent. more than those on deficient food.

Through the courtesy of a colleague we were given the opportunity to study polyneuritis gallinarum in a Rhode Island Red cock. The cause was cooked hominy. The photographs show the extreme degree of paralysis and the prompt recovery after the administration of the extract of corn chops and a diet of the same food. This animal became neuritic by a change of diet which was not extreme, and at no time was there any confinement as in the experiments above recorded. The range was sufficient for exercise and the animal had abundant opportunity to supplement the hominy with other food. This suggests other factors not yet understood which play a part in deficiency conditions.

The red-legged condition was very definite and the cause was well established. The cure was equally simple. It would be beyond the scope of this work to attempt to show that the condition was analogous to pellagra as polyneuritis gallinarum is to beriberi.

Suffice it to say that the observation was of the greatest help to us in our work, and by it we were able to determine very exactly the quality of the grain, for it was a very delicate indicator. We were disposed to regard polyneuritis as the result of a total deficiency and the red-legged condition as a partial deficiency. If this can be applied to pellagra, it is readily understood why the coolie of the East has beriberi, while in the South the deficiency disease is pellagra. The coolie eats one food and there is no chance for making up the deficiency with other foods. In the South there is always more than one food, and therefore the deficiency is made up in part at least.

Why it was impossible to produce polyneuritis gallinarum in the pigeons with the red-legged condition we cannot say. In several pellagrins we found polyneuritis which much resembled beriberi, though such a diagnosis was not ventured because of the frequency of the use of excessive dosage of arsenic in the disease. It is very probable that many cases of neuritis in pellagra have been caused in this way.

Feeling justified in the opinion that the portion of the grain removed in milling contained the vitamin, the lack of which caused pellagra, it was decided to feed pellagrins on exclusive diet of corn chops.

Case I.—A white man, aged sixty-five years. Symmetrical erythema of the backs of the hands, stomatitis, diarrhea, prostration, and amaciation. For several months the diarrhea had been troublesome, and the number of stools varied from six to ten in twenty-four hours. On Wednesday morning he was placed on an exclusive diet of corn chops, but allowed a little butter. The corn chops was baked as bread without soda or baking powder and was also made into a gruel. The patient was fed five times during the day. It was explained to him that the remedy was in the food and could not be successfully extracted. After forty-eight hours the relief was most striking: the diarrhea had ceased, the stomatitis was relieved, and desquamation was progressing rapidly. On Sunday he was discharged with only the one complaint, constipation, to be considered. He was kept under observation for several weeks in the dispensary, and there was no recurrence.

Case II.—A white man, aged fifty-six years. The backs of his hands were covered with a bullous erythema and the redness was intense. The first physician who saw him suspected a dangerous skin infection. The lesions

were perfectly symmetrical. There was a complaint of stomatitis and diarrhea. In addition the patient was a diabetic. He was placed on a diet of corn chops, and at the end of four days the skin lesions were relieved and exfoliation was progressing rapidly, the diarrhea and all other symptoms had ceased. After a few days he was given the Allen fast and treated for the diabetes, with prompt disappearance of sugar. After three months there has been no recurrence of pellagra.

Case III.—A well-conditioned white woman, aged twenty-two years. She had many peculiarities of diet, and as a result was suffering from pellagra of a typical kind. The erythema covered the backs of her forearms, and there was a classic Casal's collar. She complained of diarrhea and stomatitis. After four days of corn chops she was relieved of all symptoms, and at the end of a week desquamation was complete. After two weeks of this treatment she had gained eight pounds and felt better than in years. She was allowed other things besides the chops, but was required to eat the latter at least three times a day.

It was found that far-advanced cases were not relieved in this striking manner, though improvement often followed, and the treatment was well justified. After a time structural change takes place both in the intestinal tract and the nervous system, and no treatment can avail anything. This is equally true of other diseases, for which there are specifics.

Case IV.—A negro woman, aged about thirty years, was admitted to the hospital in a hopeless condition. She was far advanced in dementia. The bowels and bladder were being emptied in the bed, and the patient required an attendant constantly to keep her in bed. It was impossible to feed her except by the tube, which was used three times in the twenty-four hours. At each feeding a pint of milk and three eggs were given. There was some improvement, but it was not marked until 4 ounces of a gruel of wheat middlings was added. The intestinal condition improved promptly, and there would be periods of entire freedom from the diarrhea. The mental condition also improved, and the use of the tube was abandoned. The patient died rather suddenly from an unknown cause. In spite of the unfavorable termination there could be no doubt that the food caused improvement, and more markedly when the food containing grain cortex was added.

In all cases treated by the feeding method no drugs were used except an occasional placebo. It was soon learned that the corn chops to be effective must be freely milled. Just how this can be worked out practically remains to be demonstrated by some reliable

dealer. Whatever the essential substance is, there can be no doubt that it is very unstable, and apart from this, owing to the occurrence of rancidity, corn chops keeps very poorly. Some chemical process may be introduced to extract from the corn chops or the wheat middlings the essential substance. Our own efforts along this line, while proving that such a substance was present and could be extracted, were too expensive for practical purposes because of the great amount of alcohol necessary for the extraction. Mr. G. F. Catlett was able to secure 65 c.c. of a watery substance from one kilo of corn chops, but 8000 c.c. of alcohol was required. The same general plan was followed as had been formerly used in the preparation of rice polish extract. The product made in our laboratory from corn chops was certainly as effective as rice polish in polyneuritis gallinarum, when that condition was caused by defective corn. There is no reason to believe that it would not have been equally as effective if the polyneuritis had been caused by polished rice. Certainly in pellagra we were able to relieve the symptoms by the use of wheat middlings in one case and corn chops in others. This suggests that there probably is no specificity in the vitamin, but that all grains under discussion yield a certain amount, and that the only difference is one of richness.

While the larger part of our experimental work was confined to a consideration of corn deficiency, we are entirely in accord with those observers who regard the wheat as a more frequent source of the deficiency in the South at this time. We were in a position to study the corn question, and were desirous of explaining in the beginning why polenta, the national dish of the Italian peasantry, caused pellagra. It can be readily accepted now that the toxicity of Lombroso was really a deficiency, and that food forming almost the exclusive diet of the people under his observation was polenta. Polenta is a thick cornmeal mush, which was kept for days after its cooking, and which usually underwent fermentation. It has been shown that when corn is deficient the germ is usually the portion of the grain first and most seriously damaged regardless of the source of injury. Much of this Italian corn was badly damaged, and therefore was deficient because the vitamin had been destroyed in the germ. We will later study the result of fermentation on the vitamin content of polenta.

It is obvious that vitamin deficiency of the grain food may be replaced by an abundant protein as lean fresh meat, milk, eggs, and various other foods, all of which belong in the expensive class. It is also obvious that an infant may be protected from scurvy while on a faulty diet by giving such an antiscorbutic as orange juice, but is there justification for such a procedure? With the gradually increasing cost of foods of the vitamin-supplying type, the poor whites of the South find themselves no nearer their salvation from this great scourge. Lombroso once said that it would be equally as effective to advise his patient to be rich as to advise the diet needed, and if the patients were rich he would not have to advise any diet, for his natural desires would be sufficient to protect him from the disease. If decortication of grain and faulty methods of cooking cause the disease, the remedy is not beyond the reach of the poorest pellagrin. And this is our experience. It is, of course, granted that the high protein diet is most desirable, but the practical solution of the pellagra problem in the South calls for some other remedy. It can be easily shown that people live without meat, milk, eggs, and other expensive protein, and still do not suffer from pellagra. Our experience is that such people do not eat decorticated grains. We have learned also, as pointed out on a previous page, that the response from feeding pellagrins the decorticated portions of the grain is more prompt than when the diet is meat and eggs. It is to be hoped that the vitamin preparation of A. Seidel,[1] which is made from brewer's yeast, using Lloyd's reagent, will be an inexpensive source of making up the deficit in the diet of the pellagra class. We have had no opportunity to test it in the treatment of the disease.

It would appear to us that pellagra is readily prevented; that the prevention does not require any increased cost of living; that the use of whole grains that have not undergone destructive changes and the avoidance of alkaline-rising agents would entirely eradicate the disease.

It gives me pleasure to acknowledge my debt to Mr. G. F. Catlett, who by his sympathetic advice and aid in the chemical portion of this study has made it possible.

[1] Public Health Reports, 1916.

DISCUSSION

Dr. Joseph Sailer, Philadelphia, said that for a long time pellagra has been growing in importance in this country and it now needs to be kept constantly in mind by physicians in the North as well as in the South. He had recently seen two cases in Philadelphia, one in a white woman, one in a negress; both had lived in the city for thirty years; neither had ever used cornmeal as food. The etiological factors are difficult to explain: not all patients are subject to the same dietetic conditions, but all have some fundamental privation most probably. Bringing pellagra into the list of nutritional diseases, and Dr. Wood's careful work leads in this direction, gives reason to hope for its control. How may the sudden irruption of pellagra in the United States be accounted for? Was it present but unrecognized formerly? The disease is undoubtedly on the increase.

Dr. Alfred F. Hess, New York, said he was unable to discuss pellagra as a deficiency disease, but an observation in infantile scurvy might be of interest in this connection. Dr. Wood had found the corn germ curative for pellagra; he himself had found that the wheat germ alleviates scurvy; middlings have some but less effect. Another experience indicates, on the other hand, the diverse origins of deficiency diseases: beriberi and scurvy have some symptoms in common—tachycardia, nerve changes, etc. But yeast, which is specific for beriberi has no effect in scurvy.

Dr. Nathan E. Brill, New York, said his experience coincided with Dr. Sailer's. He had recently observed a man who had not been outside New York City in twelve years; he had a gastric ulcer, for which a posterior gastro-enterostomy was done. He later developed pellagra, but stated that he had never tasted cornmeal in his life.

Dr. E. J. Wood, Wilmington, N. C., said he had seen many pellagrins who had never eaten cornmeal in their lives, but who, nevertheless, were relieved by feeding them corn chops. The wheat pericarp or "middlings" will probably act in the same way. The very extensive use of baking powder and soda in the South according to Voegtlin may be a factor in the pellagra problem; these ingredients in bread may liberate enough soda carbonate to destroy the vitamines in the best of grain. It is a fact that the sudden appearance of pellagra in the South was coincident with the disappearance of the old-fashioned water-power grist mill.

LIPASE IN THE URINE OF THE TUBERCULOUS

By WM. CHARLES WHITE, M.D.

AND

PETER IVAN ZEEDICK

PITTSBURGH

(R. B. Mellon Research Laboratory, Tuberculosis League of Pittsburgh)

We undertook this study with the hope of finding some light on the mechanism which brings about two features in the course of a tuberculosis in which the animal body succumbs to the disease. The two features are the rapid disappearance of the body fat and consumption of the tubercles. Both features are part of a common process and perhaps partake of a common mechanism.

The evidence of the presence of lipase in the tubercle bacillus itself has multiplied during the past few years, *e. g.*, Wells and Corper[1] demonstrated a lipase in tubercle bacilli capable of splitting olive oil, ethyl butyrate, and triacetin; Kendal, Day and Walker[2] found a soluble lipase in the broth cultures on which tubercle bacilli had grown; White[3] and Ravenel[4] showed that tubercle bacilli could grow on such a foreign substance as paraffin; that lipase is part of the interaction between the tubercle bacillus and the body cells has been shown by Achalme[5] and Klotz,[6] who had both found lipase in the pus of tuberculous abscesses. Bauer[9] found fluctuation of serum lipase in cases of tuberculosis.

The literature on lipase in the tissues and blood has been very much augmented in the last few years, especially since the classical work of A. S. Lowenhart.[7] The outstanding facts are its abundant presence in certain tissues and the serum, its solubility, its reversible action, its excretion by the kidneys (Hewlett[8]), and its variation as a circulating content of the blood in certain diseases, especially when liver tissue is undergoing destruction (Whipple[10]).

One curious feature found by Bradley[11] is the presence of lipase in comparatively large amounts in lung tissue. This was also indicated by our own work[12] on the persistence of fat in lung tissue after intravenous injection, its retention in the endothelial cells of the lung, and its gradual disappearance.

In the present study we made 194 separate examinations of urine of normal and tuberculous humans for the presence of lipase in this excretion.

The cases were as follows:

Case C., aged thirty years. Moderately advanced tuberculosis of lungs; moderate fever; frequent hemorrhages; pneumothorax. Death two months after tests. Fever during tests, 97° to 101° F. All the urine examined during six days and other separate tests. Number of titrations for lipase, 19.

Case M. H., aged twenty-seven years. Far-advanced tuberculosis of lungs, bowel, and peritoneum. Fever, 98° to 102° F. Died nine months later. Including all urine in six days and other separate tests. Number of titrations for lipase, 28.

Case Br., aged seventeen years. Far-advanced tuberculosis of lungs, peritoneum, and colon, with cavitation. Fever, 97° to 103° F. Separate tests and tests on all urine in six days. Number of titrations for lipase, 42.

Case A., aged twenty years. Far-advanced tuberculosis of lungs; profuse sweats. Temperature, 97° to 102° F. Died two months after tests Separate tests. Number of titrations for lipase, 9.

The other examinations were separate tests on individual cases:

Tuberculosis with slight or no fever and progressing to recovery, 73.
Normal men, including 1 case of lupus, 12.
One case of pneumonia. Temperature, 103° to 105° F., 4.
One case of typhoid fever, fourth week. Temperature, 98° to 102° F., 7.

Our knowledge of lipase in the normal urine may be summed up in the conclusion of Lowenhart:[7] "The urine possesses but a trace of lipolytic activity, and at times none at all;" and of Hewlett:[8] "Very little if any lipase is present in normal urine." Our experiments on the urine of normal cases and tuberculous cases without fever verify these findings.

The method finally adopted for determining lipase in the urine is as follows: Five cubic centimeters of urine are placed in each

of three flasks. The urine in the second flask is then boiled. To the urine in the third flask are added three drops of a 1 per cent.

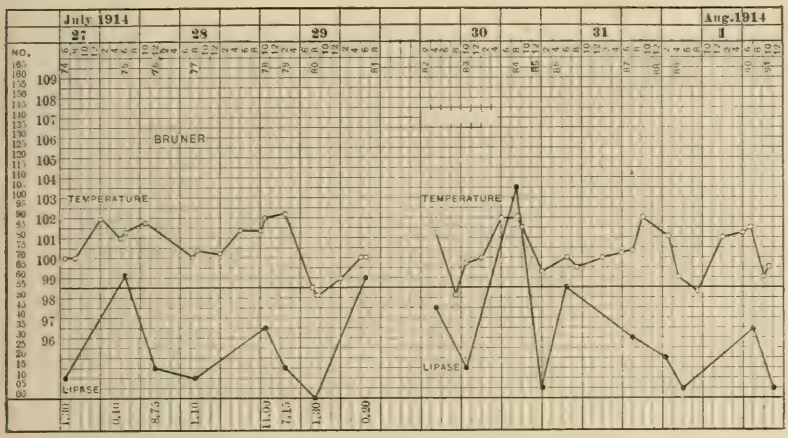

CHART I.—Far-advanced case. Cavitation, fever. Upper curve, temperature curve. Lower curve, lipase curve.

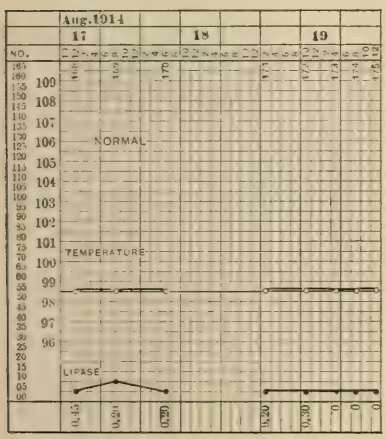

CHART II.—Two normal men. Upper curve, temperature. Lower curve, lipase.

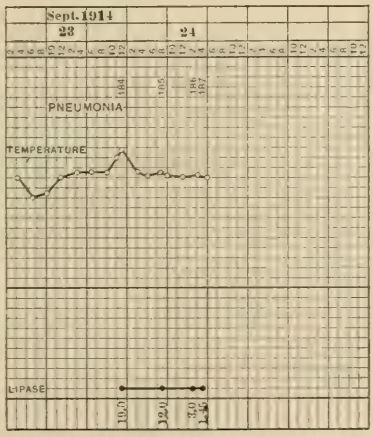

CHART III.—Pneumonia. High temperature. No lipase.

solution of phenolphthalein, and $\frac{N}{10}$ sodium hydrate solution is allowed to run in from a burette until a faint pink color appears. The amount of sodium hydrate solution used is read off and a like

amount is added to the first and second flasks. To each of these two flasks, the first of unboiled urine and the second of boiled urine, is then added 0.25 c.c. of ethyl butyrate and 0.1 c.c. toluene, and they are placed in a thermostat at 39° C. for about twenty hours. The toluene is added in order to prevent the growth of bacteria. At the end of this time each flask is taken out and sufficient $\frac{N}{10}$ hydrochloric acid is added to more than neutralize the alkali previously added by 0.5 c.c. (Hewlett[8]).

Each specimen is then shaken in a separating funnel with 50 c.c. of redistilled ether, and the ether is separated. After adding three drops of a 1 per cent. solution of phenolphthalein to 25 c.c. of pure alcohol the latter is brought to the neutral point. The ether extract from the separating funnel is now added to the neutralized alcohol and its acidity is determined by titrating with $\frac{N}{20}$ potassium hydrate solution. Any decided difference between the acidity of the ethereal extracts of the boiled and of the unboiled urine is due to the butyric acid formed by the cleavage of the ethyl butyrate; and when the difference in acidity is at all great the odor of this butyric acid can be easily recognized. This method of determining lipase in the urine is simple, and is sufficiently accurate for the amounts of lipase which occur in the urine under certain pathological conditions (Hewlett[8]).

Our findings may be summed up as follows:

1. In the urine of the normal humans and humans with tuberculosis having no fever and progressing to recovery there is very little if any lipase.

2. In the urine of the advanced cases of tuberculosis with fever and oncoming fatality there was a marked variation in the lipase content.

3. The increase in lipase content of the urine preceded and accompanied the fever and declined with defervesence. That the lipase content had no relation to intake of food or starvation was proved by examining all samples of urine emitted in 3 cases over periods of six days each.

4. There was no lipase in the urine of 1 case of pneumonia with high fever.

5. In 1 case of typhoid fever there was a slight variation in lipase content of the urine which preceded and followed the fever as in tuberculosis.

The following questions are suggested but unanswerable with the reported experiments:

1. Was the lipase added to the urine between the journey from the kidney vessels to the meatus urinarius?

2. Was the blood lipase increased during the fever with a consequent increased elimination in the urine?

3. Was the lipase increase due to fever or the fever due to increased lipase production?

4. Did the lipase increase have its origin in the tuberculous process or in the body cells generally?

5. If in the former place, is the daily variation in lipase activity the phenomenon that accounts for the characteristic daily picture of an advancing tuberculous lesion?

6. Is the lipase increase due to injury to other organs, such as the liver, by the toxins of the tuberculous process?

7. Is the tuberculous process an evidence of synthesis and hydrolysis by lipase?

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PROTEOSE INTOXICATION

INTESTINAL OBSTRUCTION, PERITONITIS, AND PANCREATITIS

By G. H. WHIPPLE, M.D.
SAN FRANCISCO

This communication deals with the etiology of the intoxication which develops in intestinal obstruction, general peritonitis, and acute hemorrhagic pancreatitis. It has been demonstrated[1] that the intoxication of intestinal obstruction is due to a primary proteose which may be precipitated by 5 volumes of 95 per cent. alcohol or by half-saturation with ammonium sulphate. It is comparatively easy to isolate the poison from closed loops of the intestine. This proteose is very toxic, and 100 mgs. may suffice to poison fatally a 15-pound dog.

Peritonitis and pancreatitis have some clinical features in common with acute intestinal obstruction. At times there may be some difficulties in differential diagnosis. We propose to show that the intoxication in these three conditions is due in large part to toxic proteoses.

There may well be other substances concerned but we believe the proteose is the most potent factor in the toxic reaction following peritonitis and pancreatitis.

When a toxic proteose is isolated from a closed loop of intestine it may be objected that this substance is not actually concerned in the intoxication. It cannot be demonstrated in the blood for example. But when a toxic proteose is isolated from the exudate of a general peritonitis no valid reason can be given why this substance is not concerned in the associated intoxication. Absorption

[1] Whipple, Rodenbaugh and Kilgore, Jour. Exp. Med., 1916, xxiii, 123.

from the peritoneal cavity is known to be very rapid and any soluble substance like a proteose will be absorbed into the blood stream with alacrity. We can show that a peritoneal exudate contains a toxic proteose which is precipitable by 5 volumes of 95 per cent. alcohol and closely resembles the proteose isolated from closed intestinal loops. It gives the same biological reaction when injected into animals.

Further, it can be shown conclusively that this proteose is not due to bacterial activity, as a toxic proteose can be demonstrated in a sterile peritonitis caused by turpentine, aleuronat, or bile. It seems safe to assume that the proteose must be derived from the proteins of the host. In a general peritonitis due to bacteria the same proteose can be isolated, and it is logical to suppose that here, too, the proteose may be derived from the tissues or tissue proteins of the host.

A sterile hemorrhagic pancreatitis may be produced by the injection of bile into the pancreatic duct. The clinical picture of intoxication under these conditions is familiar and much like that of acute intestinal obstruction. During the first twenty-four hours after the operation the animal may be killed, the pancreas rapidly ground up in water, the mixture certifugalized, and the supernatant fluid poured into 5 volumes of 95 per cent. alcohol. This percipitate contains much albumin which can be removed by heat in a faintly acid solution. The slightly opalescent filtrate can be concentrated and tested in animals to show the presence of a toxic proteose. The amount of proteose here is not great as compared with the amount in an intestinal obstruction, but this difference may be due to the great difference of rapidity of absorption. It is possible that the proteose is absorbed from the pancreas almost as rapidly as it is formed. Jobling[1] has brought indirect evidence to show that there is a proteose intoxication in acute pancreatitis.

Considerable data have been very recently published[2] to show the rise in non-coagulable nitrogen of the blood in many conditions of intoxication, especially acute intestinal obstruction. The non-coagulable nitrogen may rise from a level of 25 mgs. per 100 c.c.

[1] Petersen, Jobling and Eggstein, Jour. Exp. Med., 1916, xxiii, 491.
[2] Cooke, Rodenbaugh and Whipple, Jour. Exp. Med., 1916, xxiii, No. 6.

blood to 100 or even 200 mgs. There is no lack of eliminative power in the kidneys to account for this. Acute proteose intoxications due to the injection of a pure proteose into a normal dog may show a rise in non-coagulable nitrogen from 25 mgs. per 100 c.c. of blood to 40 to 60 mgs. within three or four hours. A similar rise in blood non-coagulable nitrogen may be found in association with general peritonitis, whether sterile or septic, and acute hemorrhagic pancreatitis.

Experiments have been carried out to explain the rise in non-coagulable blood nitrogen in these conditions—intestinal obstruction (including closed loops of intestine)—general peritonitis and acute hemorrhagic pancreatitis—also pleurisy and abscess formation. Dogs kept in metabolism cages during starvation after four or five days show a constant urinary nitrogen elimination per twenty-four hours. If a small dose of pure proteose is given intravenously, there will be a great increase in the urinary nitrogen elimination—perhaps much over 100 per cent. increase per day, and the increase lasts over three to five days. The greatest increase appears usually on the second day after injection and not during the first twenty-four hours, as would be expected. This nitrogen must be derived from the tissues of the animal, and it is to be emphasized that the katabolism and increased elimination lasts for days. The rapid rise in blood non-coagulable nitrogen may last only a few hours following the injection and is usually best seen in fatal cases where the tissue destruction is extreme. But all the evidence points to katabolism of the host's tissues due to the proteose intoxication as explaining the high non-protein nitrogen of the blood.

In like manner a dog on starvation with a uniform urinary nitrogen excretion will show a great rise in nitrogen elimination if a closed loop of intestine is produced. The rise may be much over 100 per cent. elimination per twenty-four hours and last many days. A certain type of simple duodenal obstruction can be produced with which there will be little or no vomiting and no dehydration. Such animals may show over 200 per cent. increase in urinary nitrogen elimination per twenty-four hours, and death in six to eight days may show a blood non-coagulable nitrogen well over 100 mgs. per 100 c.c. blood.

Similar experiments may be performed upon dogs with uniform nitrogen excretion when a pancreatitis, peritonitis, pleurisy or sterile abscess has been produced. The same prompt rise in nitrogen elimination will follow the inflammation. It is not to be considered for a moment that this reaction means simply a disintegration of tissue at the site of inflammation and an elimination of the nitrogen from this tissue only. We are dealing with an increase of two or three grams of nitrogen per twenty-four hours which can scarcely be accounted for by injury of the local tissue. We assume that the injury of the local tissue gives rise to toxic proteoses which are absorbed into the blood and injure the entire organism, causing among other things a considerable destruction of tissue protein in all parts of the body and the resultant increase in blood non-coagulable nitrogen, followed by a great rise in urinary nitrogen.

These toxic proteoses isolated from the intestine, peritoneum and pancreas have certain biological reactions in common but give no specific reactions by which we can differentiate them. They give no anaphylactic reactions in guinea-pigs, no precipitins, no complement-fixation. It has been shown[1] that the blood of dogs injected repeatedly with proteose cannot destroy the toxic proteose, whereas the tissues of such animals can rapidly destroy such proteoses *in vitro*.

The proteose concerned in the intoxication of intestinal obstruction is resistant to digestion by intestinal mucosa, pancreatitic and tissue ferments. We have not yet determined whether the toxic proteoses concerned in hemorrhagic pancreatitis and general peritonitis possess this same resistance to digestive enzymes.

Any animal injected with one proteose becomes resistant to this proteose but also to other proteoses. For example, proteose from human material when injected into a dog will give tolerance to any of the proteoses obtained from the intestine or peritoneum of the dog or cat. This holds for all proteoses tested by us.

It is important that dogs with long-continued obstruction or closed intestinal loops will survive lethal doses of pure proteose with but few clinical symptoms of intoxication. Also, dogs recover-

[1] Whipple, Stone, Bernhein Jour. Exp. Med., 1914, xix, 144.

ing from a sterile pleurisy or peritonitis show a definite resistance or tolerance to subsequent proteose injections. All this evidence strengthens the argument that a proteose intoxication is present in these various conditions.

Other conditions in which inflammation and pus formation or tissue destruction are conspicuous may be considered, and it is possible that toxic proteoses may be concerned. We have made experiments with sterile pleurisy, considered as identical with peritonitis, and with sterile abscess formation, but do not care to report at this time. Infarcts, pneumonia, and many other conditions are interesting possibilities which are being studied.

We feel confident that sufficient evidence has accumulated to show that there is a definite proteose intoxication in intestinal obstruction and allied conditions, in general peritonitis, either septic or sterile, and in acute hemorrhagic pancreatitis. We believe that the proteose intoxication is the most important factor in the general intoxication noted in these conditions. The detailed experiments will be published in the near future.

SOME BLOOD-PRESSURE PHENOMENA IN EXOPHTHALMIC GOITRE

By ALBERT E. TAUSSIG, M.D.
ST. LOUIS

The vascular abnormalities of well-marked cases of Graves's disease are striking and characteristic. The larger arteries pulsate violently, so that the entire body may be shaken with each cardiac systole, as in aortic regurgitation. The radial pulse has the characteristics of a *pulsus celer*, and a capillary or even a venous pulse is not rare. All gradations are found, from cases that show this typical picture to others in which the pulse shows only a moderate tachycardia.

The blood-pressure changes are much less uniform, and different observers have reported varying conclusions. Some (Hensen, Gross, Jackson, Bing, Federn) consider the systolic pressure in Graves's disease high, others (Gibson, A. Fränkel) report normal findings, while still others (Spiethoff, Donath) lay stress upon the great variability of the systolic blood-pressure in this disease. A number of experimenters have studied the effect of injections of substances derived from normal and diseased thyroids upon the blood-pressure. With considerable unanimity they report a fall of blood-pressure following such injections, but so many extraneous factors come into play in these experiments that as yet none of this work can be said to have a definite bearing upon the blood-pressure phenomena of Graves's disease.

All of the blood-pressure determinations referred to have been concerned with systolic pressures alone. Very little study has been devoted to the diastolic pressure.

As Janeway points out, "The rapidity of the pulse and the muscular tremor make estimations of diastolic pressure very difficult in these people," and he "can only record a single satisfactory one. Here the systolic pressure was 200 mm., diastolic 130 mm. (Erl. 5 cm.), pulse-pressure 70 mm., equal to 54 per cent. of the diastolic. Were all the pressures corrected for the narrow armlet, this would be about 65 per cent. In this case slight perturbation ran up the systolic pressure to 240 mm."

At the 1915 meeting of the Association of American Physicians, Plummer[1] reported blood-pressure observations in something over 2500 cases of toxic goitre. While the systolic pressure slowly rose with age, it was somewhat high on the whole, whereas the diastolic pressure was normal or even a little low. The result is a relatively high pulse-pressure exactly as found in my own small list of cases.

During the past winter I had occasion to study nine fairly typical cases of exophthalmic goitre. All of them presented the characteristic picture of the disease, and in three the diagnosis was confirmed by the histological examination of the goitre after the operation. The one case (F. H.) that presented no thyroid enlargement failed to do so because the goitre had previously been removed by operation. A number of other cases of what probably was hyperthyroidism were excluded from the series because the incompleteness of the clinical picture rendered the diagnosis uncertain.

TABLE I.—BLOOD-PRESSURE IN EXOPHTHALMIC GOITRE

Case.	Age.	Blood-pressures.			Relation of pulse-pressure to diastolic pressure.	Sounding arteries.	Capillary pulse.	Pulsating goitre.	Pulse rate (per minute).	Exophthalmos.	Tremor.	Remarks.
		Systolic.	Diastolic.	Pulse.								
		mm.	mm.	mm.	p. c.							
S. R.	37	124	62	62	100	+	0	+	70–110	+	+	
V. C.	31	125	75	50	67	+	0	+	110–160	+	+	Confirmed by operation.
D. M.	48	152	60	92	153	+	0	+	80–125	+	+	Confirmed by operation.
L. L.	35	148	88	60	68	0	0	+	95–145	+	+	Confirmed by operation.
E. M.	19	140	82	58	71	0	0	+	80–125	+	+	
E. S.	33	151	78	73	94	0	0	+	120	+	+	
E. G.	47	160	75	85	113	+	+	+	95–140	+	+	Glycosuria.
F. H.	39	150	90	60	67	0	0	0	112	+	+	Previous thyroidectomy without benefit.
S. S.	15	135	75	60	80	0	0	+	100–130	+	+	

[1] Tr. Assn. Am. Phys., 1915, xxx, 450.

As shown in Table I, the systolic pressure[1] in these cases was, on the whole, somewhat higher than in health, ranging from 124 mm. Hg. to 160 mm., and averaging 143 mm. The diastolic pressure, on the other hand, did not depart widely from the normal, ranging from 60 mm. to 90 mm., and averaging 76 mm. The result is a uniformaly high pulse-pressure, especially as compared with the diastolic pressure. Whereas the pulse-pressure in health is about 50 per cent. of the diastolic pressure, the proportion in these cases varies from 67 per cent. to 153 per cent., and averages 90 per cent. In this respect the findings coincide with those characteristic of aortic regurgitation, a result that need not surprise us when we consider the close resemblance between the other circulatory abnormalities of the two diseases. In this connection it is interesting to note that in all three of the cases that had a pulse-pressure higher than the diastolic pressure a systolic sound was audible in the larger arteries, and that one of these cases had a well-marked capillary pulse.

The two conditions resemble each other in still another respect. Hill and Flack in 1909 and Hill and Rowlands in 1912 showed that the blood-pressure readings in the arm and leg are the same in young men when lying quiet and in the horizontal posture. They also showed that the systolic pressures in aortic regurgitation were uniformly much higher in the leg than in the arm, the difference being so great and so constant that they believed it to have a diagnostic value. The similarity between the blood-pressure findings in aortic regurgitation and exophthalmic goitre made it seem well to investigate the leg pressures in exophthalmic goitre also.

The ordinary Faught arm-band, which is a trifle over 12 cm. wide, was wrapped around the thigh just above the knee and reënforced by a stout inelastic cuff. The systolic and diastolic pressures were determined, as in the arm, by listening with a stethoscope placed over the popliteal artery in the popliteal space.

[1] Most of the blood-pressure determinations were made by means of an aneroid manometer (usually the Faught, sometimes the Tycos), less often by means of a mercury manometer. The auscultatory method was used (except occasionally in the leg), the appearance of the sound on lowering the pressure in the cuff being taken to mark the systolic pressure, the dulling of the arterial sound, the diastolic pressure. Since the conclusive work of Erlanger, the method requires no defence.

The sounds were always feebler than over the brachial artery, but, being louder in exophthalmic goitre than in health, could usually be utilized for this purpose with little difficulty. Any error, due to the feebleness of the sounds, in the popliteal space, would have minimized, not magnified, the difference between arm and leg. Care was taken to have the patient relaxed and in a horizontal posture, and as free as possible from excitement. It might be supposed that the annoyance attendant upon the manipulation of her thigh might result in a rise in blood-pressure when the leg pressures were being estimated in a woman. To avoid this source of error the following procedure was adopted in all of our later cases: The blood-pressures were first determined in the arm and then simultaneously by two observers in arm and leg. The manipulation of the leg caused no rise in the arm blood-pressures, and the uniform absence of any such variation would seem to justify the inclusion of our earlier cases in which the precaution was omitted. Nevertheless it is a precaution that should not be neglected in future similar observations.

Table II shows the differences between the arm and leg pressures. The differences between the systolic pressures vary from 20 mm. to 51 mm. Hg. and average 37.3 mm. The differences between the diastolic pressures range from 1 mm. to 20 mm., averaging 7.6 mm.; those between the pulse pressures from 15 mm. to 48 mm., averaging 29.7 mm.

TABLE II.—DIFFERENCE BETWEEN ARM AND LEG PRESSURES IN EXOPHTHALMIC GOITRE. ARM BLOOD-PRESSURES SUBTRACTED FROM LEG BLOOD-PRESSURES

Case.	Systolic, mm.	Diastolic, mm.	Pulse, mm.
S. R.	49.0	1.0	48.0
V. C.	45.0	20.0	25.0
D. M.	51.0	7.0	44.0
L. L.	37.0	6.0	31.0
E. M.	30.0	8.0	22.0
E. S.	24.0	8.0	16.0
E. G.	50.0	10.0	40.0
F. H.	40.0	6.0	34.0
S. S.	20.0	5.0	15.0
Average	37.3	7.6	29.7

The systolic differences and the pulse-pressure differences in arm and leg are definite and characteristic phenomena, and, as determined, are more apt to be too low than too high. The same

cannot be said with certainty of the diastolic pressures. In some of the cases the feebleness of the sounds in the popliteal space made it impossible to be quite certain whether the sound did not become inaudible before the fourth phase was reached, thus leading to an unduly high estimation of the diastolic pressure. This was particularly true of the second case (V. C.), in which the difference in diastolic pressure was recorded as 20 mm. In other cases, however, the sounds in the popliteal space were loud and ringing, so that the dulling of the arterial sound could be placed accurately. Here, too, a slight but definite difference between the diastolic pressures in arm and leg could be made out.

Another point deserves mention: In the first, second, third, and seventh cases (see Table I) the arterial sound persisted down to zero pressure in the cuff. According to the view that the onset of arterial silence marks the point of diastolic pressure, the latter cannot be determined in such cases. The dulling of the sound is, however, always well marked in such cases, and, as shown by Taussig and Cook, under similar circumstances, in aortic regurgitation, can be taken with confidence as the diastolic pressure.

For purposes of comparison, the arm and leg pressures were estimated, with the same technic, in a few unselected cases of aortic regurgitation. As shown in Table III, the differences between the arm and leg pressures, while on the whole greater in aortic regurgitation than in exophthalmic goitre, are of the same general order of magnitude.

Table III.—Difference between Arm and Leg Pressures in Aortic Regurgitation

Case.	Systolic pressure differences, mm.	Diastolic pressure differences, mm.	Pulse pressure differences, mm.
1	43	6	37
2	50	10	40
3	66	4	62
4	35	10	25
5	58	10	48
6	85	5	80
7	30	0	30

Five cases of what were probably non-toxic goitres were studied (Table IV). In three of them (I. M., F. D., and M. W.) a tentative clinical diagnosis of atypical Graves's disease was made. The

histological examination of the excised tissue, after partial thyroidectomy, showed in two cases a "colloid goitre," in the third a "cystadenoma" of the thyroid. Another case (A. S.) had been diagnosed elsewhere as atypical exophthalmic goitre. A careful study of the patient, together with the subsequent course of the case, led to the belief that this diagnosis was mistaken.

TABLE IV.—ARM AND LEG BLOOD-PRESSURES IN NON-TOXIC GOITRES

Case.	Age.	Limb.	Pressures.			Relation of pulse-pressure to diastolic pressure.	Pulse rate (per minute).	Remarks.
			Systolic.	Diastolic.	Pulse.			
			mm.	mm.	mm.	p. c.		
I. M.	15	Arm	135	85	50	59	65–104	Large goitre; no marked tachycardia; inconstant tremor; marked nervousness; histological diagnosis after thyroidectomy: "colloid goitre."
		Leg	136	85	51			
F. D.	..	Arm	135	85	50	59	70–80	Goitre; moderate tachycardia; marked nervousness; no response to thyroid feeding; histological diagnosis after thyroidectomy: "cystadenoma."
		Leg	135	85	50			
A. S.	22	Arm	150	100	50	50	104	Cystic goitre; tachycardia; marked nervousness; no other evidence of hyperthyroidism.
		Leg	153	100	53			
J. G.	11	Arm	130	64	66	106	80–110	Small hard goitre; marked exophthalmos; no tachycardia; no tremor; no response to thyroid feeding.
		Leg	130	64	66			
M. W.	39	Arm	133	82	51	62	85–100	Firm, non-pulsating goitre; questionable von Graefe; slight tremor; no definite tachycardia; histological diagnosis after thyroidectomy: "colloid goitre."
		Leg	135	82 (?)	51 (?)			

In the fourth case (J. G.) the diagnosis remains uncertain. The patient, a girl, aged eleven years, has a small, hard, nodular goitre and very marked bilateral exophthalmos. There is, however, no tachycardia, no tremor, no nervousness, no response to thyroid feeding. Her blood-pressure, on the other hand, shows the relatively high pulse-pressure (higher than the diastolic pressure) found in our cases of true exophthalmic goitre. All of these five cases show identical pressures in arm and leg.

CONCLUSIONS. 1. The blood-pressure abnormalities of exophthalmic goitre are the same in kind, though not quite in degree, as those characteristic of aortic regurgitation. The pulse-pressure is high, as compared with the diastolic pressure. The systolic and pulse-pressures in the leg are uniformly and considerably higher than those in the arm.

2. The non-toxic goitres studied show no such difference between the arm and leg pressures, but, on the contrary, show a striking identity between the blood-pressures in the upper and lower limbs.

3. The diagnostic value of a higher blood-pressure in the leg than in the arm can easily be overestimated. A study, not yet concluded, of the relative pressure in the arm and leg in a variety of diseases shows that this difference characterizes a variety of affections, in particular the hypertension of chronic interstitial nephritis and acute endocarditis. It may, however, be that the finding of identical pressures in arm and leg may help to exclude the presence of a true exophthalmic goitre.

THE FUNCTION OF THE THYROID, NORMAL AND ABNORMAL[1]

By HENRY S. PLUMMER, M.D.
ROCHESTER, MINN.

The thyroid performs its function so silently that but little regarding this function has been learned from the study of normal persons. Information has come from the manifestations associated with congenital, traumatic or pathological loss of the thyroid, or the evidence of excessive thyroidization associated with pathological thyroids and thyroid feeding.

It is my purpose to present a mass of clinical and pathological data so correlated as to support or refute many of the theories regarding goiter and thyroid function. I have found it necessary in abstracting to leave out statistical data, omitting to discuss the theories and presenting such alternate hypotheses as the facts suggest. I will therefore present here the entire abstract as hypothetical, leaving the segregation of facts and theories for the paper to be completed later.

The function of the thyroid is to furnish a hormone essential to cell metabolism. The clinical syndromes known as hyperthyroidism and hypothyroidism are the evidence of the departure of the individual from the normal attending deficient or excessive metabolism dependent upon this hormone. Sustained fluctuations in these reactions within limits that do not give rise to recognizable clinical syndromes may damage the individual. This may explain the goiter heart, in some cases unattended by definite evidences of

[1] Abstract, as recent developments in the knowledge of thyroid function make it seem desirable to rearrange the data for later publication.

hyperthyroidism. On this ground also may be built a theory that associates essential hypertension with and without goiter.

The normal thyroid never gives rise to definite clinical evidence of excessive or deficient function. The myxedematous patient can be so readily changed from the vegetating to an active intellectual organism that hypothyroidism, as a landmark in deficient thyroid function, can be passed almost without comment. Definite clinical evidence of excessive thyroid function is seen only as it accompanies goiter. Goiter, as the term is commonly employed, is an enlargement of the thyroid due, primarily, to an increase in the number of acini (adenomatosis); in the size of the acinar cells (hypertrophy); in the number of cells per acini (hyperplasia) or the intra-acinar content. These changes are due to stimuli applied to the parenchyma cells and are, in the main, indicative of a functional activity above normal. The increased blood supply demanded by a hyperfunctioning parenchyma may materially add to the size of the gland. Increase in the intra-acinar cells, secondary and degenerative changes that may lead to increase in the size of the gland will not be considered further than to mention the probability that inflammatory and degenerative changes may at times stimulate the function of the thyroid as a whole.

On a correlation of clinical and pathological data, we may assume that there are two factors, or groups of factors, leading to goiter in man. As this grouping is primarily, though by no means wholly, based on the association of the clinical evidence of excessive function and hypertrophy, we may for convenience designate the first, the major stimulus; the second, the minor stimulus. Wherein these stimuli or the factors accompanying them differ in degree, type, source or association, is open to question. That normal stimuli play an important part in the development of goiter can hardly be doubted. I will discuss in the paper, but only mention here, that colloid and adenomatous goiter are prone to develop when increased metabolism from normal physiological causes makes a demand on the thyroid above the mean.

The parenchyma of postnatal thyroid is constituted of functioning colloid-containing acini, plus in an unknown percentage of persons, fetal acini. Application of the major stimulus to either fully de-

veloped or fetal tissue results in demonstrable hypertrophy, hyperplasia and the hyperthyroidism characteristic of exophthalmic goiter. In this condition the highest degree of hypertrophy probably represents the height of thyroid productivity. Hyperplasia results when the stimulus is forcing the cell above its capacity which may be limited by beginning exhaustion from overwork, lack of material for its product, etc. Hypertrophy and hyperplasia may be coexistent in the thyroid or an acinus, though it is not probable that the cell can hypersecrete when undergoing division.

The minor stimulus applied to prenatally developed colloid-containing acini results in a hypertrophy of lesser degree and hypersecretion, or hypersecretion without at least a readily demonstrable increase in the size of the cell. Colloid is deposited in excess. This constitutes the colloid goiter. Rarely hypertrophy is marked and it is possible that hyperplasia may supervene. This hypertrophy and hyperplasia may be present without accompanying clinical evidence of hyperthyroidism, and does not give rise to the syndrome of exophthalmic goiter.

The application of the minor stimulus to the fetal acini results: (1) In the formation of new acini (?); (2) functioning of the acini; and (3) hyperfunctioning of the acini with or without the deposit of colloid above the normal with or without demonstrable hypertrophy. Whatever the inception of the adenomatous process, the acini once active seem, in the main, to functionate and follow the same pathogenetic laws as the acini of colloid goiter. In a small area of glands may be seen all types of acini—from the fetal without a lumen to the hypertrophic and hyperplastic. It is the inclusion of fetal acini and the arrangement of sustentacular tissue to be expected from the development of new gland mass from belated fetal rests, rather than the character of the functioning acini that distinguishes adenomatous thyroid. This lower grade adenomatous tissue is more sensitive to stimulation, as is evidenced by its greater tendency to hyperfunctionate and degenerate.

That the same stimulus applied to fully developed thyroid and fetal thyroid will result respectively in colloid goiter and adenomatous goiter, correlates with clinical observation. This is based largely on the incidence of simple colloid and adenomatous goiter

throughout the decades of life and the incidence of hyperfunction in the two types (data will be included in the published paper).

The known products of the thyroid are: colloid and its hormone, the alpha iodin compound of Kendall. The thyroid secretes into its acini (externally) colloid, iodin and perhaps its hormone. It secretes into its circulatory channels (internally) colloid and alpha iodin. The time relation of these two phases cannot be definitely pointed out but it seems probable that while one or the other is prone to predominate, they may be coincident. Whether the phases be coincident or alternate, the sum total of alpha iodin delivered into the circulation during a prolonged period in which colloid is being deposited, is in excess. The deposition of colloid in excess is in the main indicative of a hyperfunctioning gland. This does not imply that the degree of activity can be determined by the amount of colloid present at the time of its removal. It may somewhat further elucidate the conception to apply the term "cystic" to acini which as an immediate result of the degenerative changes are functionless or relatively functionless retention pockets.

The normal thyroid studied histologically is a relatively dormant appearing gland. Under mean conditions the amount of its hormone required is small; it is probable that it does not have to fluctuate rapidly to meet unusual demands, and that there is relatively little change in its intra-acinar content. The greater part of the alpha iodin may be supplied by simply remodeling the molecule returned from the tissue but little changed in its metabolic function. The goitrous thyroid may have long periods when its function is not above the normal. We cannot recognize histologically the hyperfunctioning gland except as hypertrophy is present.

It is self-evident that stimulation of the thyroid will not result in excessive production of its hormone if iodin is not available. Lack of available iodin and strong coincident stimulation may be one of the factors in producing hyperplasia. The work of Marine, Bensley and others suggest that this is true of the hyperplasia of dogs, opossums, etc. It is not probable that the administration of iodin ever reduces the output of the thyroid hormone. It will increase it if the previous supply is not in excess and the thyroid is under high stimulation. In the paper I will present evidence to support

the concept that the administration of the thyroid hormone will put the gland at relative rest, provided the demand is not above the capacity of the gland. These concepts afford a reasonable basis for correlating the many discordant results following the administration of iodin and thyroid to goitrous man and animals.

The majority of cases of colloid goiter have their inception between the fifteenth and eighteenth years; are prone to give clinical evidence of excessive function from the seventeenth to twenty-first years; again enlarge with the high metabolism of pregnancy and with or without the clinical evidence of hyperthyroidism, give rise to a damaged heart between the thirty-fifth and fortieth years. After the fortieth year, 27 per cent. of the cases coming to the consultant have blood-pressure readings attributable to arterial hypertension. During the periods of increased functional activity, the parenchyma may show demonstrable histological evidence of cell hypertrophy. High degrees of hypertrophy are unusual.

Adenomatous goiter follows much the same course. It is less apt to be accompanied by hyperthyroidism previous to the thirtieth year; after the thirtieth year it gives rise to much higher degrees of hyperthyroidism than does colloid goiter, and this without hypertrophy of the parenchymal cells. The incidence of exophthalmic goiter gradually rises to the thirtieth year and then falls to the sixtieth year. Colloid and adenomatous goiter predispose but slightly, if at all, to exophthalmic goiter, though the stimulus that gives rise to the hypertrophy of the latter will also stimulate the development of adenomas.

That the thyroid plays an important part in metabolism and that the evidence of high metabolism dominates the clinical syndrome of hyperthyroidism is generally recognized, but to what extent the conception of others approach that of the author, is indeterminable from literature—namely, that the rate of metabolism is dependent upon the thyroid hormone, that this function is not specific for certain tissues, but is common to all the cells of the organism. Increase or decrease in the rate of the metabolism dependent upon this hormone to a sufficient degree gives rise to the clinical syndromes of hypothyroidism and hyperthyroidism. The normal thyroid undoubtedly responds to relative exhaustion of its hormone by the

metabolic activity stimulated largely by nervous impulses. The correlation of the physiological reactions characterizing the syndromes clinically recognized as hyperthyroidism and that of these reactions, with the histopathology of goiter, must to a certain extent remain hypothetical until we are able to determine the conditions under which they are attributable to a primary excess of the thyroid hormone or a primary high rate of metabolism demanding this hormone.

However, without this knowledge, an analysis of these syndromes alone leaves little, if any, ground for doubting that the rate of metabolism in the tissues is dependent upon this hormone. In the paper I have attempted to discuss in detail the data in support of this theory. I will only mention here that we have learned to recognize and determine the degree of hyperthyroidism on the local evidence of a hyperfunctioning thyroid and the physiological reactions attributable to stimulation, depression or degeneration of the more highly differentiated fundamental tissues of the organism.

Prominent, but less easily analyzed, are the reactions in the secretory tissues. Here the direct action of the hormone is overshadowed by the functional activity supporting the metabolism of the more fundamental tissues. A conception of the physiological pathology of exophthalmic goiter can be visualized in a general way by multiplying all of the normal physiological reactions, taking into consideration the exhaustion and degenerative changes that would of necessity result.

STUDIES OF THE ACTIVE CONSTITUENT, IN CRYSTALLINE FORM, OF THE THYROID

By EDWARD C. KENDALL, Ph.D.
ROCHESTER, MINN.

About eighteen months ago I reported the isolation from the thyroid of a crystalline compound containing 60 per cent. of iodin. Since that time I have perfected the method for its isolation, and to some extent have studied its chemical properties and function. The work may be briefly summarized as follows:

The compound was first isolated in crystalline form in 1914. The work just prior to the isolation had been accomplished with such ease and success that no difficulty was anticipated in repeating it, but despite most persistent efforts, more crystals were not isolated until August, 1915. Again it seemed that the isolation had been perfected, but try as we would, no more crystals were seen until February, 1916. This failure occurred in spite of the fact that the work was vigorously carried on, more than a ton of thyroid material being used. It was found by accident that carbon dioxid is essential for the separation of the compound. When I first obtained the substance I was working in a room next to a freezing microtome and the necessary carbon dioxid was supplied from this source. Later the work was continued in a room free from excessive carbon dioxid, and crystals were not obtained until it was accidentally discovered that carbon dioxid is necessary.

The reason for the delay and difficulties in this problem lies in the fact that the substance does not exist in a free form in the thyroid secretion, but is firmly locked within the protein molecule. This bond is so secure that it will withstand very vigorous chemical treatment. Under some conditions the iodin compound is very

FIG. 1.—Crystals of the alpha iodin compound, which is the active constituent of the thyroid.

FIG. 2.—Appearance of patient upon entering clinic.

FIG. 3.—After six months' treatment with the alpha iodin compound. Patient had grown three and a half inches.

Fig. 4.—Appearance of patient upon entering clinic.

Fig. 5.—After six months' treatment with the alpha iodin compound.' Patient had grown three and a half inches.

FIG. 6.—Appearance of patient upon entering clinic.

FIG. 7.—After eighteen days' treatment, during which time patient received a total of less than one-third of a grain of alpha iodin compound.

FIG. 8.—Appearance of patient upon entering clinic.

FIG. 9.—After eighteen days' treatment, during which time patient received a total of less than one-third of a grain of alpha iodin compound.

FIG. 10.—Appearance of patient upon entering clinic.

FIG. 11.—After twenty-four days' treatment, during which time the patient received the alpha iodin compound.

FIG. 12.—Appearance of patient upon entering clinic.

FIG. 13.—After twenty-four days' treatment, during which time the patient received the alpha iodin compound.

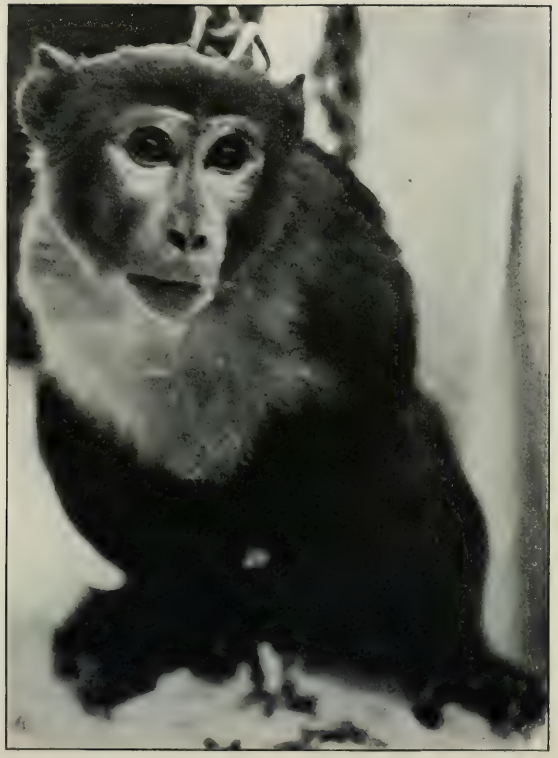

FIG. 14.—Normal monkey before injection. Weight, thirteen and a half pounds.

FIG. 15.—Same monkey after seventy-two daily injections of one and a half milligrams of alpha iodin compound. Weight, six pounds.

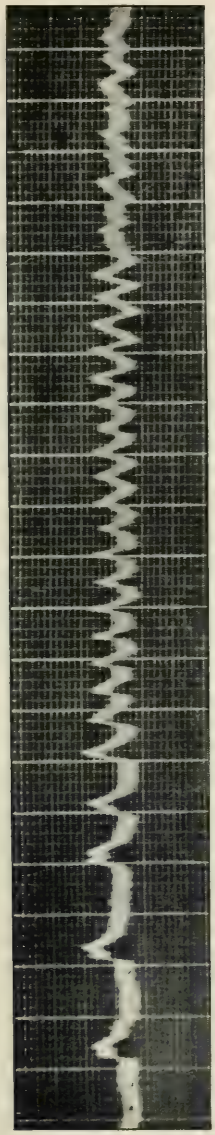

Fig. 16.—Ventricular fibrillation of a goat's heart produced by eleven successive daily injections of the alpha iodin compound. Pulse rate 100.

resistant and is not easily destroyed, but under other conditions it is extremely sensitive. Carbon dioxid exerts a peculiar and unique action on the bond that ties the iodin compound within the protein

molecule. In short, this bond which resists heating with 50 per cent. sodium hydroxid is broken by carbon dioxid and the iodin compound is set free. Having once liberated the compound from the rest of the protein constituents, its chemical properties permit a simple method of separation.

Having separated the crystalline compound containing 60 per cent. of iodin from the thyroid, several questions arise as to the relation of this compound and thyroid activity. Thyroid activity can be followed experimentally and clinically in five broad aspects, namely, the effect on growth, the mentality, the skin, the hemoglobin, and, greatest of all, on metabolism. Incident to the change in metabolism is the effect on the heart. It seems indisputable that the physiological activity of the thyroid is produced through its effect on metabolism. The combustion of proteins, fats, and carbohydrates is increased by the administration of thyroid substance, and it is probable that the various clinical changes produced are due to the increase in cell activity throughout the body. The mentality is affected because of the increased blood flow and the increased metabolism going on in the brain cells. The condition of the skin is improved because metabolism within the skin cells is increased; and so it is throughout the entire body.

We have experimented with this substance on animals, and have made a large number of clinical observations. The activity of the thyroid is manifested by the administration of this crystalline compound alone. There appears to be no other substance in the thyroid secretion which acts directly to produce hyperthyroid symptoms. This substance, given even in very small amounts, relieves the conditions of myxedema and cretinism, and in excess produces symptoms simulating those of exophthalmic goiter. It appears to have no specific action on the pulse rate. The extent to which the rate is affected depends, not on the administration of the thyroid alone, but on many other factors. The effect may be outlined as follows:

After the administration of the compound there is no apparent change for many hours. There is no increased pulse rate nor drop in blood-pressure. However, if the thyroid hormone and certain metabolits (amino acids) are injected simultaneously, the pulse rate

may be enormously affected, and even death may result, due to the greatly increased rate of metabolism going on in the animal. It appears very probable that the thyroid hormone manifests its activity by reacting with amino acids. The accompanying are typical pictures which illustrate the effect on myxedema and cretinism, on the mentality, on the skin, and the great emaciation with a toxic effect on the heart after long-continued injection (Figs. 1 to 16).

THE PATHOLOGIC CHANGES IN THE SYMPATHETIC SYSTEM IN GOITER

By LOUIS B. WILSON, M.D.
ROCHESTER, MINNESOTA

The amount and character of the pathologic changes in the sympathetic ganglia removed at operation or at autopsy from patients with exophthalmic goiter have been studied by other observers meagerly and rarely by modern methods. I have reviewed elsewhere[1] the literature of previous reports. So far as the findings have been positive, they have shown that in exophthalmic goiter the cells of the sympathetic ganglia exhibit various stages of degeneration. The paucity and incompleteness of the reported observations, however, together with Cannon's[2] recent experimental production of some of the symtpoms of exophthalmic goiter in cats by constant stimulation of the thyroid through the sympathetic system, have warranted a more careful study of the material accumulating in the Mayo Clinic.

Previous Report in the Present Series of Observations. Durante and I[1] have recently reported our observations on twenty superior cervical sympathetic ganglia removed at operation from sixteen patients with hyperplastic toxic (exophthalmic) goiter. Our findings may be briefly summarized as follows:

1. Definite histologic changes in the cells of the cervical sympathetic ganglia in hyperplastic toxic (exophthalmic) goiter occurred in all cases examined.

2. These histologic changes consisted of various stages of degeneration, namely (*a*) hyperchromatization, (*b*) hyperpigmentation,

(*c*) chromatolysis, and (*d*) atrophy or (*e*) granular degeneration of the nerve cells.

3. Some of the ganglia contained cells resembling the partially differentiated cells found in the ganglia of infants.

4. Accompanying the more advanced changes in the ganglion cells were similar degenerative changes in the nerve fibers and an increase of connective tissue throughout the ganglion, but especially in the outer and middle coats of the vessels and in the periganglionic tissue.

5. So far as could be determined from the small number of observations, the pathologic changes in the cervical sympathetic ganglia were parallel to the stage and intensity of the symptoms of hyperthyroidism and to the hyperplastic and regressive changes in the thyroid.

Material for the Present Study. The present report is based on a study of the cervical and other sympathetic ganglia removed at autopsy from twelve patients dying during the course of exophthalmic goiter. The observations have been controlled by similar studies on sympathetic ganglia removed at autopsy from nine patients dying of diseases other than exophthalmic goiter, and by studies on Gasserian ganglia removed at operation from six patients with trifacial neuralgia.

All ganglia removed at operation were fixed within five minutes after removal, and the material from autopsies was fixed within three hours after death. Some portions of ganglia were examined in frozen sections of the fresh tissue. The remainder of the specimen or specimens was fixed in 10 per cent. formalin. Selected blocks were cut frozen without embedding, and the sections stained with Sudan III or by Nissl's method. Other blocks were embedded in paraffin and cut in serial sections, which were stained with hematoxylin-eosin, by Weigert-van Gieson's method for connective tissue, by Weigert-Luden's method for myelin,[3] and by Held-Nissl's method for distribution of chromatin. Other blocks were used for silver impregnation by Ramon y Cajal's,[4] Levaditi's[5] or Bielschowsky's methods. Others were fixed and stained by Bensley's[6] acetic-osmic-bichromate method for mitochondria. The most satisfactory results were obtained by the use of Sudan III, Held-Nissl's, Ramon y Cajal's and Bensley's stains.

PROTOCOLS

Case I (A-156,845).—The patient was a female, nineteen years of age, who had had severe symptoms of hyperplastic toxic goiter for five months. Recently the thyroid had enlarged very rapidly. The patient died of hyperthyroidism a few days after coming to the Clinic, without having been operated on. At autopsy, three hours and forty minutes after death, there was found marked hyperplasia of the thyroid, marked exophthalmos, symmetrical brown pigmentation of the conjunctivæ, marked emaciation, petechial hemorrhages in the skin, in the parietal peritoneum of the true pelvis, and elsewhere in the pelvic organs, marked hypertrophy of the myocardium of the left ventricle, slight nodular sclerosis of the coronary arteries, and fatty changes in the intima. The thymus weighed 80 grams.

Microscopically, the thyroid showed progressive advanced hypertrophy and hyperplasia, Type B.[7] The superior cervical ganglia showed very marked hyperpigmentation and extensive granular degeneration of the cells, many of which were atrophic or consisted of only small masses of pigment.

Case II (A-153,535).—The patient was a female, nineteen years of age; for five months had shown symptoms of severe exophthalmic goiter. Her systolic blood-pressure was 180, diastolic 75, with a pulse-rate of 150 to 168. After two weeks' preparation the left superior thyroid vessels were ligated. The temperature remained normal and the pulse fluctuated from 100 to 118. Three days after operation she died. The macroscopic findings at autopsy, made three hours and fifteen minutes after death, were those of severe exophthalmic goiter.

Microscopically, the thyroid showed progressive advanced hypertrophy and hyperplasia, Type B.[7] Many of the cells from the cervical sympathetic ganglia were in the state of advanced degeneration noted in Case 1, though not nearly so many cells were affected (Fig. 1).

Case III (A-144,809).—A female, thirty years of age; had had severe symptoms of exophthalmic goiter for eight months. At the time of examination her systolic blood-pressure was 165, diastolic 70, and pulse-rate 128. The left superior thyroid vessels were ligated and four months later the right superior thyroid vessels were also ligated. Two weeks after the second ligation the right lobe, isthmus, and pyramidal lobe of the thyroid were extirpated. She died the following day. At autopsy, two hours and thirty minutes after death, an advanced chronic myocarditis with fatty degeneration and advanced degenerative changes in the liver and kidneys were found.

Microscopically, the thyroid showed early regressive advanced hypertrophy and hyperplasia, Type C–1[7]. In the cervical sympa-

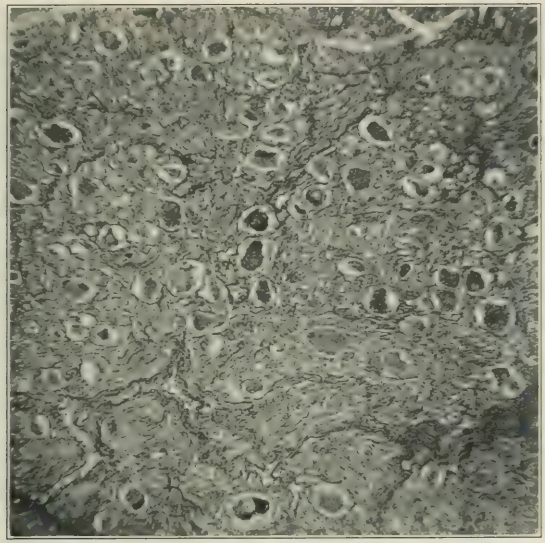

FIG. 1 (Case II).—Section of left superior cervical sympathetic ganglion, silver impregnation, 5 microns. × 120 diameters. Advanced degeneration of many cells.

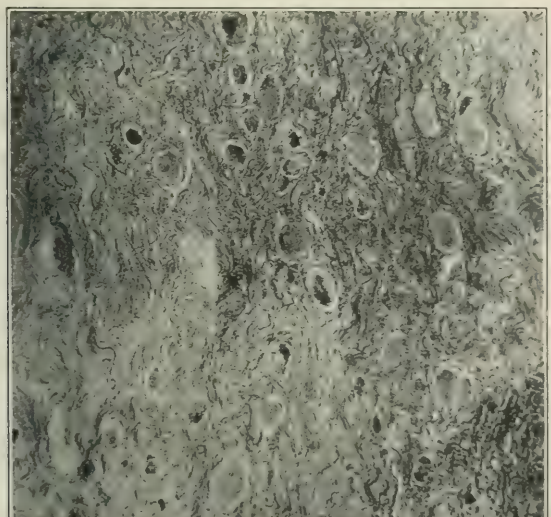

FIG. 2 (Case III).—Section of left superior cervical sympathetic ganglion, silver impregnation, 5 microns. × 120 diameters. A few normal cells, many showing advanced degeneration.

thetic ganglia, a few cells were apparently normal. Many showed varying degrees of hyperpigmentation and granular degeneration (Fig. 2).

Case IV (A-136,418).—The patient, a female, twenty-five years of age, had shown symptoms of exophthalmic goiter for two years, with marked increase in severity during the last three weeks. At the time of examination the systolic blood-pressure was 145, and the diastolic 80. The left superior thyroid vessels were ligated, and five days later the right superior vessels were ligated also. Four and a half months later the right lobe, isthmus, and a small portion of the left lobe of the thyroid were resected. The patient died nine days after the operation. At autopsy, eight hours after death, the macroscopic findings were a hypertrophied thymus, acute myocardial degeneration, and dilatation of the heart, congestion and degeneration of all parenchymatous organs, and severe purulent bronchitis. The cervical sympathetic ganglia were noticeably enlarged.

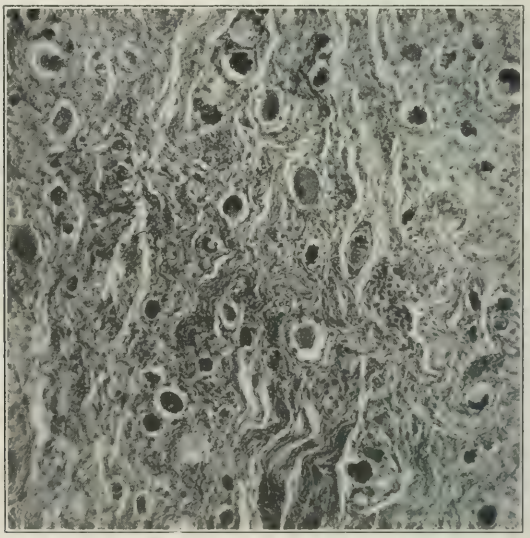

Fig 3 (Case IV).—Section of right superior cervical sympathetic ganglion, silver impregnation, 10 microns. × 120 diameters. A few normal cells, many in varying stages of degeneration.

Microscopically, the thyroid showed early regressive advanced parenchymatous hypertrophy and hyperplasia, Type C–1[7]. The ganglia showed a few fairly normal cells, but many others in varying stages of degeneration (Fig. 3).

Case V (A-11,264).—This patient was a female, thirty-three years of age, who had had symptoms of exophthalmic goiter beginning two years and five months previously. At the time of examination the systolic blood-pressure was 138, diastolic 90, and pulse-rate 138. The left superior thyroid vessels were ligated, and two weeks later the right superior thyroid vessels were ligated. Two and three months after the last ligation, hot-water injections were made into each lobe of the thyroid, and three weeks after this, or four and a half months after the first ligation, the right lobe and isthmus of the thyroid were extirpated. The patient's pulse-rate increased to 140, and she died twenty-four hours after the operation. At autopsy, two hours and thirty minutes after death, the principal macroscopic findings were acute and chronic myocardial degeneration, with a dilated heart, general parenchymatous degeneration not so severe as usual in exophthalmic goiter, and chronic nephritis.

Microscopically, the thyroid showed early regressive advanced hypertrophy and hyperplasia, Type C–1[7]. A few cells in the cervical sympathetic ganglia were normal. Many showed varying degrees of hyperpigmentation and granular degeneration.

Case VI (A-149,095).—The patient, a female, twenty-eight years of age, had shown symptoms of exophthalmic goiter for six years, with a maximum severity within the first year. At the time of examination she had slight exophthalmos, a systolic blood-pressure of 150, a diastolic of 80, and a pulse-rate of 120. The left superior thyroid vessels were ligated, and two weeks later hot-water injections were made into the right lobe of the thyroid. One week after this the right superior thyroid vessels were divided and the ends ligated separately. Two weeks after the last operation the patient died. At autopsy, one hour after death, the principal macroscopic findings were bilateral lobar pneumonia with infarction of right upper lobe, and hypertrophy and dilatation of the heart.

Microscopically, the thyroid showed a regressing advanced hypertrophy and hyperplasia, Type C–2[7]. The cervical sympathetic ganglia showed many cells apparently normal, a few in advanced stages of degeneration, and a very few in intermediate stages of degeneration.

Case VII (A-135,172).—The patient, a female, twenty-nine years of age, had had goiter for sixteen years with moderate symptoms of thyrotoxicosis for twelve years, the maximum severity of toxic symptoms having been attained about four years ago, since which time there had been some abatement. At the time of examination the systolic blood-pressure was

175, the diastolic 78, and the pulse-rate 114. The left and right superior thyroid vessels were ligated, and four months later the right lobe, isthmus, and a small piece of the left lobe of the thyroid were extirpated. The patient died one week after operation. At autopsy, two hours after death, the macroscopic findings were an hypertrophied thymus, bilateral emphysema, acute splenitis, and chronic nephritis, with congestion.

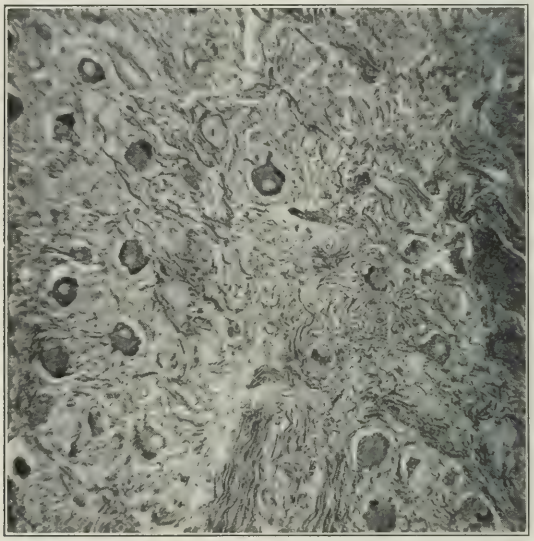

FIG. 4 (Case VII).—Section of right superior cervical sympathetic ganglion, silver impregnation, 5 microns. × 120 diameters. Marked reduction in the number of cells, many apparently normal, and a few in advanced stages of degeneration.

Microscopically, the thyroid showed advanced regressive changes on chronic hypertrophy and hyperplasia, Type C–2[7]. The superior cervical sympathetic ganglia showed many cells apparently normal and a few in advanced stages of degeneration. The total number of cells was apparently much reduced (Fig. 4).

CASE VIII (A-109,170).—This patient, a female, forty-seven years of age, had noticed enlargement of the thyroid for four years, but with symptoms ascribable to thyrotoxicosis, beginning only one year prior to the enlargement. At the time of examination the systolic blood-pressure was 140, diastolic 45, and pulse-rate 120. The right and left superior thyroid vessels were ligated. The patient improved steadily in health for eight or nine months, and then began to lose appetite, weight, and strength. A year after the first operation, several hot-water injections into the thyroid were

made. The patient's general health improved, but her blood-pressure rose to 166 systolic, 90 diastolic, and pulse-rate to 140 six months after the injections. One month later her pulse-rate had risen to 176. A month after this, or one year and eight months after the first operation, she died. At autopsy, three hours after death, the macroscopic findings were hypertrophy and dilatation of the heart, chronic cholecystitis, and parenchymatous degeneration of all organs.

Microscopically, the thyroid showed advanced regression on an old parenchymatous hypertrophy and hyperplasia, Type C–3[7]. The superior cervical sympathetic ganglia showed a great reduction in the total number of cells, many of the remaining ones of which, however, were normal while a few were in advanced stages of granular degeneration.

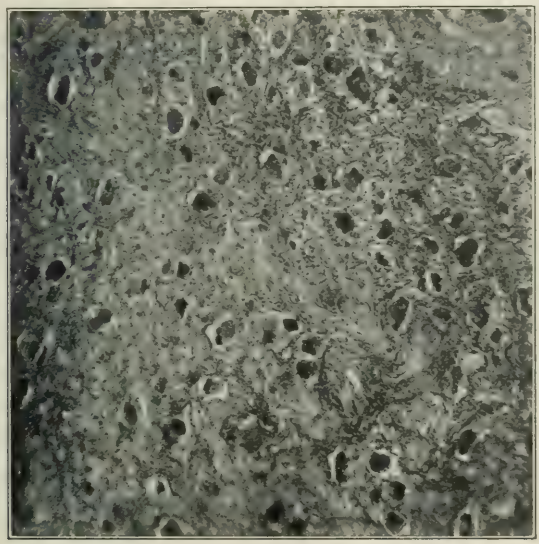

FIG. 5 (Case IX).—Section of right superior cervical sympathetic ganglion, silver impregnation, 10 microns. × 120 diameters. Many normal cells, many hyperpigmented, and a few in advanced stages of degeneration.

CASE IX (A-147,479).—The patient, a female, forty-four years of age, had had thyroid enlargement for thirty-two years, with symptoms of thyrotoxicosis, beginning five years ago and gradually increasing to the present time. At the time of examination she had lost weight from 150 to 114 pounds. Her systolic blood-pressure was 122, diastolic 80,

and her pulse-rate was 120. She died without operation. At autopsy, two hours and forty-five minutes after death, the macroscopic findings were a medium-sized retrotracheal thyroid, hemopericardium, and right hemothorax with adhesions, and acute parenchymatous degeneration with fatty changes in the heart, liver, kidneys, and chronic nephritis.

Microscopically, the thyroid showed advanced regression on chronic parenchymatous hypertrophy and hyperplasia. Type C–3[7]. The superior cervical sympathetic ganglia showed a marked reduction in the total number of cells present. Of those present, many were normal, and a few were in advanced stages of degeneration (Fig. 5).

Case X (A-67,759).—The patient, a female, fifty years of age, had had enlargement of the thyroid for twenty years, with mild symptoms of thyrotoxicosis beginning coincident with the thyroid enlargement and lasting for three years. Six months previous to examination, the symptoms of thyrotoxicosis returned. At the time of examination, the patient was emaciated, the pulse-rate was 200, with a cardiac arrhythmia growing progressively worse. She died three days after examination. At autopsy, one hour after death, the principal macroscopic findings were enlarged thyroid, myocarditis, atrophic and fatty changes in the liver, and chronic nephritis.

Microscopically, the thyroid showed advanced regressive changes in parenchymatous hypertrophy and hyperplasia with some adenomatosis, Type C–3[7]. The superior cervical sympathetic ganglia showed a marked reduction in the total number of cells. Most of those present, however, were fairly normal while a few showed advanced degenerative changes.

Case XI (A-156,404).—The patient, a female, fifty-five years of age, had had thyroid enlargement for twenty-four years. A thyroidectomy of the right lobe was done six years before, followed by a remission of all symptoms until a recent onset of cardiac distress. At the time of examination she had lost weight from 150 to 135 pounds; had a systolic blood-pressure of 158, and a diastolic of 88. The left lobe of the thyroid was extirpated and the internal jugular on the left side ligated. The patient died three days after operation. At autopsy, two hours and thirty minutes after death, the macroscopic findings were marked acute edema of the glottis, moderate hypertrophy of the myocardium of the left ventricle, marked disseminated nodular thickening of the aorta and of the aortic and mitral valve leaflets, and a moderate sclerosis of the coronary arteries.

Microscopically, the thyroid showed advanced regression of a moderate hypertrophy and hyperplasia, with considerable adenomatosis, Type C–3[7]. The superior cervical sympathetic ganglia showed a marked reduction in the total number of cells. Of the cells present, many were normal, but a large number were in varying stages of advanced regeneration. There was marked increase of fibrous connective tissue in the ganglia (Fig. 6).

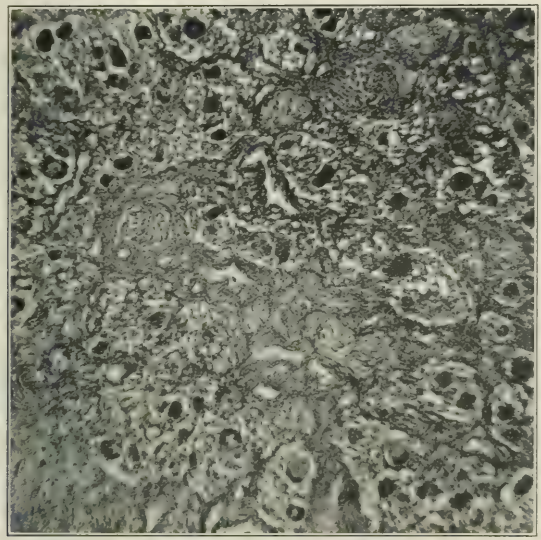

FIG. 6 (Case XI).—Section of left superior cervical sympathetic ganglion, silver impregnation, 10 microns. × 120 diameters. Marked reduction in the number of cells, many normal, and many in varying stages of advanced degeneration; marked increase of fibrous connective tissue.

SUMMARY OF PROTOCALS

A study of the preceding protocols shows that of the 11 patients, 7 were females between nineteen and thirty-nine years of age and 4 were females between forty-eight and fifty-five years of age.

When considered in relation to the duration and stage of the symptoms of exophthalmic goiter the cases may be roughly grouped into three classes:

A. Cases still presenting active progressive symptoms of hyperplastic toxic (exophthalmic) goiter. These are as follows:

1. (A-156,845) Female, aged nineteen years, symptoms five months, severity 3.*

2. (A-153,535) Female, aged nineteen years, symptoms five months, severity 2 to 3.

3. (A-136,418) Female, aged twenty-five years, symptoms two years, severity 3.

4. (A-144,809) Female, aged thirty years, symptoms eight months, severity 3.

B. Cases in which the severity of the symptoms of hyperplastic toxic goiter had partially subsided, though the acute toxic condition was yet present. These are as follows:

5. (A-11,264) Female, aged thirty-three years, symptoms two years, present severity 2.

6. (A-149,095) Female, aged twenty-eight years, symptoms six years, severity 3.

C. Cases in which the acute toxic symptoms had almost, if not completely, subsided. These are as follows:

7. (A-135,172) Female, aged thirty-nine years, goiter for sixteen years, maximum severity four years ago 3, present severity 1.

8. (A-109,170) Female, aged forty-eight years, goiter four years, symptoms five years, present severity 1.

9. (A-147,479) Female, aged forty-nine years, goiter thirty-two years, symptoms for two years, present severity 1 to 2.

10. (A-67,759) Female, aged fifty years, goiter for twenty years, symptoms during first three years of goiter, then remission until during last six months, present severity 1.

11. (A-156,404) Female, aged fifty-five years, goiter twenty-four years, thyroidectomy right lobe six years ago for doubtful exophthalmic goiter, remission until recent onset of cardiac distress.

The first 4 cases may be grouped with 5 others previously reported in which only the ganglia removed at operation were examined. In these 9 cases of acute progressive hyperplastic toxic goiter, there was very marked hyperpigmentation with extensive granular degeneration, and in some cases atrophy of the ganglion cells.

Cases 5 and 6 may be grouped with three operative cases previously reported.[1] These 5 cases showed considerable hyperpig-

* On a scale of 1 to 5, in which 5 represents the greatest severity.

mentation and granular degeneration, though a smaller number of cells were involved than in the ganglia from the cases of the first group.

Cases 7, 8, 9, 10 and 11 may be grouped with 6 other previously reported[1] operative cases. These 11 cases all showed a very marked regression or complete absence of toxic symptoms at the time of operation or death. In the ganglia from all of these the hyperpigmentation and granular degeneration affected a relatively small percentage of the cells present. In many of the cases, however, a marked diminution in the total number of cells present in the ganglion was shown by sections in series including the entire ganglion.

Discussion. Thus it will be seen that, roughly, the degree of hyperpigmentation, the amount of granular degeneration, the atrophy and the reduction in the number of cells was in direct relation to the continuation and subsequent remission of the symptoms of hyperthyroidism. Parallel with this, the perivascular connective tissue and the connective-tissue stroma generally throughout the gland were increased in direct ratio to the time during which the symptoms of hyperthyroidism had continued. In two of the cases, there was marked sclerosis of the ganglionic connective tissue.

Though the present number of cases is too small from which to draw positive conclusions, the observations so far seem to indicate that early in acute hyperplastic toxic goiter, there is present in the superior cervical, and probably also in some degree in the other sympathetic ganglia, a process which is causing active stimulation, overfunction and progressive stages of degeneration in the ganglionic cells. As the symptoms of exophthalmic goiter regress, evidence is found in the ganglia of the cessation of this degenerative process in the ganglionic cells not previously changed past recovery. After the acute toxic symptoms have entirely ceased for years, there remains little evidence of the destroyed ganglionic cells, most of the fatty pigmentary remains of the cells apparently having been absorbed.

The problems of the pathologic changes in the sympathetic ganglia in man have been obscured in the past by the occasional

presence of pigment in the ganglion cells from patients who had exhibited no symptoms of involvement of the sympathetic system. Normally, the cells of the sympathetic ganglia in man are relatively free from pigment until adult life. They then may acquire more or less extensive deposits of brown pigment granules, arranged crescentrically about the nuclei. The ganglion cells of patients dying of prolonged wasting diseases, such as tuberculosis and cancer, are apt to show an increased amount of pigmentation and in some instances varying stages of degeneration, hyperchromatization, chromatolysis and granular degeneration. As control material in these respects many ganglia have been studied by methods parallel to those used on the ganglia from the goiter cases.

Controls. The control autopsy material is as follows:

1. (A-139,228) Eight months' fetus. Placenta previa; atelectasis. Ganglionic cells normal; no pigmentation.

2. (A-138,548) Eight months' infant. Pneumonia, following operation for hare-lip. Ganglionic cells normal; no pigmentation.

3. (A-149,999) Female, aged seventeen years. Pituitary tumor. Death following puncture of corpus callosum. Dilatation of heart; acute nephritis; fatty liver. The lymph spaces around the ganglionic cells are much dilated; the cells are shrunken and hyperchromatic, but not pigmented nor degenerated.

4. (A-139,228) Female, aged thirty-six years. Placenta previa; mother of fetus Case 1. Normal; no pigmentation nor degeneration of the cells of the cervical ganglia.

5. (P. B. H. No. 61) Male, aged thirty-four years. Acromegaly; colloid goiter. No pigmentation and no degeneration in ganglia found.

6. (A-149,288) Male, aged thirty-five years. Congenital cystic kidneys; hematuria. Some pigmentation, but no degeneration of the ganglionic cells.

7. (38 P. B. H. 3289) Male, aged thirty-eight years. Acromegaly. Some hyperchromatolysis and hyperpigmentation; no granular degeneration of cells found.

8. (A-136,199) Male, aged fifty-two years. Carcinoma of anterior wall of stomach; acute parenchymatous nephritis. Autopsy five hours after death. Considerable pigmentation of ganglion cells; no degeneration.

9. (A-134,342) Male, aged sixty-four years. Carcinoma of stomach; coronary sclerosis; myocarditis; chronic nephritis. Pericellular lymph spaces of ganglia dilated; cells shrunken; feeble staining; little pigmentation; no degeneration.

The operative control material consists of Gasserian ganglia removed from six patients with trifacial neuralgia in the Mayo Clinic, and from one patient in the Peter Bent Brigham Hospital, and one cervical sympathetic ganglion removed in the Mayo Clinic because of its apparent involvement in a male patient fifty years of age in whom the primary lesion had been a persistent branchial cyst. Although the Gasserian ganglia in the 6 cases of trifacial neuralgia and the cervical sympathetic in the branchial cyst cases, were all the subject of ganglionic or periganglionic chronic inflammatory changes, and although the patients were from forty-one to seventy-one years of age, in none of the ganglia was there found evidence of such extensive degeneration of the ganglion cells as in the cases of exophthalmic goiter. In all the cases, there was more or less increase of pigment over that found in the ganglia of young adults, but in no case was the amount comparable with that found in exophthalmic goiter cases. Destruction of the ganglionic cells was apparently absent.

Thus, it is suggested that neither advanced age, chronic wasting disease nor chronic inflammatory processes necessarily cause degenerative changes in the sympathetic ganglia resembling those in exophthalmic goiter.

Involvement of Other Ganglia. The question is suggested whether the involvement of the superior and middle cervical sympathetic ganglia in exophthalmic goiter is but a part of a general metabolic disturbance evidenced by similar changes in the sympathetic ganglia elsewhere in the body, or whether it is confined to the cervical sympathetic ganglia alone. In only 4 cases in which the cervical sympathetic ganglia were shown to be involved have we been able to study the ganglia from other portions of the body. In none of these was there positive evidence of involvement other than hyperpigmentation. There was little or no granular degeneration present resembling that found in the middle and superior cervical sympathetic ganglia. These observa-

tions will, of course, need to be confirmed by a much larger series of cases, but they suggest that the ganglionic changes in exophthalmic goiter may be confined largely to the cervical sympathetics, and that they may not be a secondary result of a general metabolic disturbance.

Experimental Work. With a view to determining the possible relationship of the lesions in the sympathetic ganglia to exophthalmic goiter, studies have been made of the ganglia in a number of animals (dogs, goats, spermophiles, rabbits and monkeys), in some of which many of the symptoms of exophthalmic goiter had been produced by the administration of Kendall's[8] alpha-iodin compound, in others which had been subjected previously to double thyroidectomy, and in others in which the cervical ganglia had been injected with various bacteria. In only one animal, however, were suggestive degenerative changes found in the ganglionic cells. In this animal, a young male goat, a small amount of a virulent broth culture of Bacillus bronchisepticus (the bacillus associated with canine distemper, and an organism which frequently affects the central nervous system) was injected into the right superior cervical ganglion. The animal died twenty-four days later, and necropsy was performed within an hour after death. The superior cervical sympathetic ganglion from the left side and the stellates from both sides were all apparently normal. The right superior cervical sympathetic, which had received the injection, showed at the immediate site of the injection a small area in which the ganglionic cells were completely destroyed and replaced by necrotic tissue. Throughout the remainder of the ganglion, the cells were highly pigmented and showed various degrees of advanced degeneration. In fact, the lesions were quite parallel with those in the cervical ganglia removed from patients with acute exophthalmic goiter.

These experiments are being repeated, and will be made the subject of a subsequent report.

In conclusion, I wish to thank Professors Wm. T. Councilman, Harvey Cushing and Walter B. Cannon of Harvard Medical School, for kindly permitting me to examine their ganglionic material from autopsies, operations and animal experiments.

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CONDITIONS AFFECTING SECRETION OF THE THYROID GLAND

By W. B. CANNON, M.D.
BOSTON

A study of the conditions of activity in the ductless glands, which pass their secretions into the blood stream, is difficult because recognition of the secretion in the blood is uncertain or impossible. It has long been known that physiological activity is accompanied by the development of an electrical difference which may be manifested by connecting an active part with an inactive part through a delicate galvanometer. It seemed possible that by the application of this method important information might be obtained as to the conditions of activity of the ductless glands. This work has been carried on through the coöperation of Mr. McKeen Cattell.

The method was first justified by applying it to the submaxillary gland which has an external secretion. Because an electrical change accompanies the secretion of saliva even though the blood supply is shut off from the gland or the flow through the duct is stopped, and because the change is absent when secretion is absent, although each of the conditions attendant on secretion—such as contraction of bloodvessels, relaxation of bloodvessels, faster flow of blood, slower flow of blood—may severally be induced, the conclusion is drawn that the electrical change is a manifestation solely of the process of secretion.

The direction of this electrical current of action developed by the submaxillary gland may be reversed, although the physiological responses to stimulation remain as usual. Reversal is not, therefore, a certain sign of a reversed process in the gland.

When the action current indicates a maximal activity of the submaxillary gland excited by stimulating the sympathetic nerve in the neck (cat), the electrical response can be augmented by stimulating the chorda tympani nerve, and *vice versa;* sympathetic impulses are ineffective during the height of an effect produced by injected adrenin, and chorda tympani impulses cause no increase of the action current, while pilocarpine is strongly operative.

The method thus justified on the submaxillary gland has been applied to the thyroid. Histologists have described nerve fibers leading to the cells of this gland, and anatomists have reported that the fibers going to the thyroid gland arise in the cervical sympathetic ganglia. Previous investigators have shown that severance of its cervical sympathetic nerves causes atrophy of the thyroid, and stimulation of these nerves causes a diminished iodin content of the gland. Severance of the vagus nerve supply has no effect.

If the thyroid gland and neighboring indifferent tissues are connected through a galvanometer, stimulation of the sympathetic strand high in the thorax evokes an action current after a latent period varying usually between five and seven seconds. This effect persists after the superior and the recurrent laryngeal nerves are severed. Experiments have shown that the nerve impulses pass out through both the superior and inferior cervical ganglia.

Stimulation of the main trunk of the vagus nerve in a curarized animal, or injection of pilocarpine which excites vagus endings, has no effect in producing an action current in the thyroid gland.

The influence of sympathetic impulses is not indirect through local anemia of the gland, for when the blood supply is wholly stopped by clamping the bloodvessels for a period equal to that of sympathetic stimulation no noteworthy electrical change is produced.

The conclusion is drawn, therefore, that the nerves distributed to the thyroid cells belong to the sympathetic and not to the vagus supply, and that their effects are not indirect through alterations of blood flow; indeed, that they are true secretory nerves.

It is known that the internal secretion of the adrenal gland, or

adrenin, will have the same effect in the body as sympathetic nerve impulses. Injection of a small dose of adrenin, 0.1 to 0.2 c.c (1 to 100,000) evokes a marked action current in the thyroid gland. Also, stimulation of the nerves to the adrenal gland so as to cause their secretion to be poured into the blood stream will evoke a characteristic electrical change in the thyroid. This electrical change does not occur if the return of blood from the abdomen is prevented, but takes place promptly when the pent blood is released. Furthermore, it fails to appear after stimulating these nerves if the adrenal glands have been previously removed. There is thus definitely established an influence of adrenal secretion on thyroid activity.

This conclusion has been confirmed by the observations of Dr. Robert L. Levy working in the Harvard Laboratory. He has found that both stimulation of the cervical sympathetic trunk and injection of stimulating doses of adrenin greatly augment the effects of small doses of adrenin in raising blood-pressure. This increase of efficacy of adrenin is not produced if the thyroid glands have previously been removed.

Previous studies have shown that the adrenal glands are aroused to special activity in times of emotional stress. The thyroid gland is subject to that division of the nervous system which is brought into action in emotional excitement and which causes adrenal secretion. It is probable, therefore, that the thyroid, like the adrenal, normally has functions which are performed in times of critical emergency. It may be that such an emergency function is an exaggerated form of the routine activity of the gland.

LEUKEMIA, PSEUDOLEUKEMIA AND HODGKIN'S DISEASE

By C. H. BUNTING, M.D.
MADISON, WIS.

AND

J. L. YATES, M.D.
MILWAUKEE, WIS.

The diseases which have as their most prominent feature a progressive enlargement of the lymph nodes form a group which offers many difficulties in differential diagnosis. These difficulties beset not only the clinician but also the pathologist. In fact, it may be said that if the ordinary form of glandular tuberculosis be excluded, there is left a group of diseases which have so many common factors that separation into its component members is but a matter of opinion. This has led to a variety of attempts at classification with results, acceptable as a rule, only to the originator.

The common factors in these diseases, as we have observed them, are in brief as follows:

1. The presence (or history) of a primary focal inflammatory lesion, usually, but not necessarily, in the upper part of the digestive or of the respiratory tract (teeth, tonsils, adenoid tissue, sinuses, bronchi).

2. Progressive enlargement of the lymph nodes, with or without accessory extranodal tumors.

3. Chronic course, with late moderate secondary anemia and with the constant development of a fever, usually of an irregularly intermittent character, exceptionally of the Murchison type.

4. Eventual fatal termination within a relatively brief period of years (two to five).

5. The occurrence during the course of the disease of either the blood picture described by Bunting[1] as the primary blood picture of Hodgkin's disease, or of a leukemic blood picture.

6. The occurrence of a primary lesion in the germinal centres leading to an early loss of architecture in the lymph nodes through an extensive proliferation of diverse cells but with common factors in the picture.

7. The constant occurrence in the lesions (nodal and extranodal) of organisms of the diphtheroid type.

The group possessing these common features includes the diseases ordinarily designated as Hodgkin's disease (lymphogranulomatosis), leukemia of lymphatic type, pseudoleukemia, lymphosarcoma, malignant lymphoma, chloroma, leukosarcoma, etc., showing a nomenclature as varied as the classifications. One's first reaction after coming in contact with various members of the group is to wonder if the same effort which has been applied to the separation of the members of the group had been applied in an attempt to bring them together, would it not have increased our understanding of them? In other words, are not their resemblances greater than their differences?

In general the blood picture is held sufficient to separate one group of these cases as specific diseases under the name leukemia. This does not seem to us justifiable. The evidence from our series of cases, even though they be few, seems to indicate that the leukemic blood picture is an incidental feature in the course of the disease, or rather an individual reaction to a stimulus which in another case may fail to produce the same reaction. It seems impossible to tell clinically whether or not a patient has a leukemic blood picture. Pseudoleukemia and leukemia are indistinguishable without blood examination. This was apparent to us in a case recently published as to its cultural findings,[2] a case apparently the counterpart of that published by Wende.[3] With all the clinical signs of leukemia the patient showed the Hodgkin blood picture until his departure from observation during the last weeks of his life. Owing to this

[1] Johns Hopkins Hospital Bulletin, 1914, xxv, 173.
[2] Bunting and Yates, Johns Hopkins Hospital Bulletin, 1915, xxvi, 376.
[3] American Journal of the Medical Sciences, 1901, cxxii, 836.

departure we are unable to say whether, as in Wende's case, a terminal leukemic picture was developed.

In 3 cases of so-called pseudoleukemia we have seen the Hodgkin blood picture occur over months and in 1 case over years. In a fourth case, seen by the courtesy of Dr. Warfield at the Milwaukee County Hospital, the Hodgkin blood picture was succeeded before the patient's death by the picture of acute lymphoblastic leukemia.

The occurrence of a leukemic picture in Hodgkin's disease is apparently relatively rare. However, in 1 case sufficiently under our control, so that all data necessary for accurate diagnosis were obtainable, there occurred a change of blood picture from the secondary polymorphonuclear leukocytosis of the intense type of the disease to a leukemic picture. With a count of 72,000 leukocytes 65 per cent. were of the mononuclear type, both large and small, but atypical and immature. Some of the cells showed mitotic figures. The occurrence in the blood smear of megalokaryocytes suggested that this was a bone-marrow reaction. The picture later reverted to its original type shortly before the death of the patient, who showed at postmortem examination the lesions of acute Hodgkin's disease. In 2 other cases diagnosed clinically as Hodgkin's disease (and in one confirmed by gland excision) there appeared in blood smears submitted to us the formula of chronic lymphocytic leukemia but without apparent marked leukocytosis. We have observed also in a monkey, inoculated with diphtheroid bacilli, the occurrence of a similar picture (99 per cent. lymphocytic forms, 1 per cent. polymorphonuclear) without apparent increase in number of leukocytes. In another human case, one of acute lymphoblastic (or possibly myeloblastic) leukemia, we have seen the picture of acute leukemia develop through the Hodgkin blood picture.

Moreover, we find that it is equally as difficult to tell, from the pathological study of the lymph glands in this group of diseases, whether or not the patient had a leukemic blood picture. The glands in a case of malignant lymphoma are identical in appearance with those in chronic lymphocytic leukemia. There is no difference between the infiltrations in the large-celled acute leukemic picture

and those in lymphosarcoma or pseudoleukemia. In each case one finds with an increase in size, a loss of glandular architecture and a diffuse infiltration with the type of cells chiefly involved. It is with such observations in mind that the leukemic blood picture seems to us of incidental importance in the disease in which it occurs.

Pathological study of the glands in these cases shows, as we have just suggested, that in each there is a progressive increase in size, with early loss of architecture. The increase in size is due to a general proliferation of cells which show to a certain extent diverse types. Recognizing the common factors we may, nevertheless, make three broad groupings of the cases even at the risk of earning the censure passed on others who have attempted to classify the group.

In the first class, that of Hodgkin's disease proper, one recognizes a lesion in which destruction of lymphocytes is dominant, but in which proliferation of fibroblasts and of the reticulo-endothelial cells is prominent. This proliferation is atypical, leading to giant-cell formation. One may recognize three terminal pictures in this group.

1. Almost complete sclerosis (typical fibroblast proliferation).
2. Sarcomatoid picture (atypical fibroblastic proliferation).
3. Endotheliomatoid picture (atypical endothelial proliferation, usually with marked giant-cell formation).

The last two have the local histological picture of malignancy but without invasion (or but slight) and without tendency to form metastasis or recurrence.

In the second main group of cases we find a large-celled proliferation infiltrating the whole gland. This apparently begins with a marked proliferation of the large cells of the germinal centres, a proliferation which is atypical and which fails also to show the differentiation into lymphocytes. In very early cases there may be a thin collar of lymphocytes about these extremely large germinal centres. In cases slightly later there are architectural indications of very large germinal centres but no lymphocytes, and ultimately there is a general infiltration of the gland with these large cells and obliteration of the normal architecture. There may be some fibroblastic proliferation and giant cells may be found. From the

character of the predominant cell this might be termed the lymphoblastic group.

In the third group there is a diffuse proliferation of the small lymphocyte with very early loss of architectural landmarks. Scattered lymphoblasts and atypical endothelioid cells may occur. This may be spoken of as the lymphocytic group.

While we thus make pathological distinctions between broad groups, they are not always clear-cut. The fibroblastic proliferation and giant-cell formation may be so marked in the latter groups that a transition picture toward that of Hodgkin's disease is seen. In fact, we have no desire to separate the groups but rather to consider them as a varied reaction to the same or to similar stimuli. Were it not for the rapid course of acute leukemia (both myeloblastic and lymphoblastic) we should be inclined to see in these cases examples of the general pathological law that a toxin stimulates in mild doses (lymphoblastic and lymphocytic groups) but in strong doses destroys.

The above discussion embodies our conclusions even before we had found that culturally diphtheroid organisms could with careful technic be obtained from the glands in all of these conditions. This finding has been very abundantly confirmed by the work of others. There seems to be no question as to the constant occurrence of the organisms, but only a question as to the significance to be attached to their presence in the lesions. The majority of investigators have concluded that the organism occurs in too diverse conditions to be of etiological importance.

While we can ask only for a Scotch verdict at the present time, evidence which points toward their etiological significance from our experience is in outline as follows:

1. The constant occurrence of the organism in Hodgkin's disease and in the allied group under discussion. This is true not only for single determination but for repeated examinations, as for example, seven successful cultures from 1 case over a period of five years (neck, groin and axilla).

2. The occurrence of the organism where it would explain the lesion. We may cite as examples, its occurrence, as reported, in the cutaneous nodules in a case of acute pseudoleukemia; and the

occurrence of the diphtheroid as the only stainable organism below the surface and distributed in mucosa and submucosa in two cases of primary intestinal Hodgkin's.

3. The occurrence of the so-called Hodgkin blood picture in the whole group of cases enumerated in laboratory animals (monkey, rabbit) inoculated with the living organism and in one normal individual inoculated with the dead organisms (vaccine).

4. The occurrence of abscesses in laboratory animals (monkey, dog, rabbit, guinea-pig, horse) at the portal of inoculation with lymph-gland changes similar to those seen in early Hodgkin's disease.

5. The occurrence of complement-deviation by use of patient's serum and diphtheroid organisms (unpublished series of experiments of Yates and Kristjanson).

6. The occurrence of glandular reaction and of skin reaction in patients injected with immune serum resulting from the use of a diphtheroid antigen.

Such evidence we believe would be accepted as indicating etiological significance for almost any organism except members of the diphtheroid group. It is accepted for organisms almost as widely distributed as the diphtheroids. We must admit that the final test, the production of a disease in animals comparable to the human type, has not been accomplished. The attempt to produce a chronic disease in animals less susceptible than man (in whom the virulence is not great in the majority of cases) has resulted usually in lowering the resistance of the animal to organisms more acutely fatal. However, even here death has not occurred before the regional lymph glands have developed definite changes similar to those shown early in the group of diseases under discussion.

This question, however, must apparently be temporarily unanswered without, however, disturbing in the main our contention as to the general relationship of the diseases discussed.

DISCUSSION

Dr. H. G. Wells, Chicago, said that in studying mice in the course of tumor work, a lymphatic condition, indistinguishable from leukemia

and pseudoleukemia in man, had been repeatedly observed. Nothing exactly like lymphogranulomatosis or Hodgkin's disease had been found, although there are many obscure forms of lymphatic and splenic hyperplasia. Dr. Slye has found that the true leukemia and pseudoleukemia in mice occur only in strains that have tumors, and in heredity studies these diseases behave exactly as the true neoplasms. They have not been inoculated into normal mice in spite of many attempts. These observations support the views of those pathologists who maintain that leukemia and pseudoleukemia are tumors of the leukoblastic and lymphoblastic tissues.

Dr. Theodore C. Janeway, Baltimore, said that while we all recognize the value of Dr. Bunting's contributions to the blood pictures of the leukemias, he felt that our understanding of these conditions is not advanced by claiming that a diphtheroid organism is always present, nor by explaining contradictory findings on the basis of technical errors. He cited studies made in Baltimore of all sorts of lymph nodes without the finding of the diphtheroid organism with any degree of constancy.

Dr. Frank Billings, Chicago, said that studies had also been made in Chicago of lymph nodes from Hodgkin's disease and other lymphatic diseases: in forty-odd cases the diphtheroid organism had been recovered from all except two. But the same organism had been found in goiters, in joints, in tuberculous glands, etc.; so that he was inclined to the belief that it is a parasitic organism accidentally present in pathological tissue. Animal experiments with the organism had not indicated any specificity; and he did not believe it had any etiological relation to the lymphatic diseases.

Dr. C. H. Bunting, Madison, Wis., said the time at his disposal was too short to give all the evidence upon which he based his belief in the specificity of the diphtheroid organism. With regard to Dr. Wells' interesting remarks, he had, following the publications of Drs. Wells and Slye, questioned whether or not the individual variation in reaction in the group of diseases under question might be due to a variable inheritance—tumor or non-tumor.

POLYCYTHEMIA TREATED WITH RADIUM

By JOSEPH SAILER, M.D.
PHILADELPHIA

The treatment of splenomegaly with polycythemia has not up to the present time been entirely successful. A number of methods have been tried which may be divided into four general groups. The first is venesection; second, the application of various rays either to the spleen or the long bones; third, the administration of drugs; and fourth, splenectomy. Venesection has been generally employed on the ground that it has at least a temporary palliative effect, but even if repeated at fairly regular intervals it has failed to produce any permanent effect. A multiplicity of drugs has been employed. Of these the nitrites serve to relieve some of the symptoms. There are contradictory reports regarding the use of mercury and iodides. Latrielle has suggested citrate of sodium. McLester is given credit for suggesting benzol, of course, after it had been used in leukemia. Mellon has used nitrites and benzol together with asserted good results. The absence of the general employment of any of these remedies indicates that they have not proved very successful. Splenectomy has usually been fatal within a few days after it has been performed. There is a record of one case that lived seventeen months, dying then of tuberculosis. In this case the subsequent history leads to a suspicion that there might have been some leukemia. At any rate seven months after operation the red cells were about 2,000,000, many of them nucleated. There were 55,000 leukocytes with a large proportion of myelocytes. The results reported from the use of the Roentgen ray are contradictory. Lucas gives a very complete summary

of this method and has found three cases markedly benefited and six cases not benefited by its use. It was usually applied to the spleen. In one of Lucas's own cases it was applied over the long bones without benefit.

I wish to report a case from memory that I observed some years ago. The notes unfortunately have been lost, but my recollection of the important features is trustworthy. A Russian Jew, aged fifty-five years, consulted me for dizziness and headache. He was distinctly cyanosed. On physical examination everything was negative except the spleen, which extended about 10 cm. below the costal margin in the line of the axillary fold. The shape was rounded. The surface was smooth and the consistency firm. It could be moved palpably bimanually. For some reason that I cannot now recall I advised him to have *x*-ray treatment to the spleen. This was carried out and the man received altogether forty treatments with what I now would believe was a rather weak apparatus. His blood count before the treatments was made several times and ranged between six and seven million. The leukocytes were normal and the hemoglobin 100 +. The headaches and dizziness improved very rapidly. The spleen was slightly reduced in size. The blood count remained slightly above 5,000,000. About two years later the man was admitted to the University Hospital on the service of Dr. James Tyson and came under my care, as I was then one of Dr. Tyson's assistants. He had had an attack of intense pain in the epigastrium. The symptoms of subdiaphragmatic abscess were present and an operation was performed; the abscess was found and drained, but the patient did not survive. An autopsy was not permitted. This patient was apparently relieved for a period of two years by the application of the *x*-ray.

The case that forms the subject of this paper is as follows:

Mrs. J. B. L., white, aged fifty-five years, has had four attacks of peritonitis, the last eighteen years ago, at which time the right ovary was removed. She has also had attacks described as inflammation of the ovaries. She has suffered at times from asthma. She has suffered from severe headache for years. When she goes to a high altitude these headaches are relieved. Ten years ago, while in China, she had an attack of dengue fever. She

has had three children, all now alive and well, and two miscarriages, possibly induced. The climacterium occurred at the age of forty-one years, at which time the headaches became more severe. When first seen she was suffering from frequent headaches of a very severe type; a racking, unproductive cough; constant dyspnea and palpitation. The appetite was poor. There was often morning nausea and vomiting, with severe retching. The bowels were constipated. Nocturnal micturition occurred two to five times, and this and the dyspnea caused her to sleep very poorly. For some years the conjunctivæ have been reddened and the skin dusky. Enlargement of the spleen was first detected at the age of fifty years, while in India, but it had probably, in the patient's opinion, existed for some time. It is and has always been painless.

Polycythemia with splenomegaly had been first diagnosed by Dr. Alfred Stengel, who had had her treated by the application of *x*-ray to the long bones. The effect, if any, was slight; in the opinion of the patient she was made distinctly worse. That is, the headaches, dyspnea, nausea, and vomiting became, if possible, more severe. The physical examination was as follows: Weight, 119.12 pounds. Height, 5 feet 1 inch. Blood-pressure, 115 and 72. There was the characteristic dusky redness of the skin, acrocyanosis, deep, dusky red mucous membranes. The heart and lungs were normal; the peripheral lymph glands not enlarged. The abdomen was asymmetrically enlarged, particularly on the left side. The measurements of the spleen as nearly as they could be determined were 22 cm. in length and 22 cm. in breadth; it extends from the 8th rib in the left posterior axillary line to 1 cm. below the anterior-superior spine of the ileum and 1 cm. to the right of the median line.

In addition to the counts the following tests were made on the blood: Slight hemolysis occurred outside the rather narrow limits, 0.5 per cent. and 0.55 per cent. sodium chloride solution. There was some irregularity of the red cells, polychromatophilia, no basophilic degeneration, no nucleated reds. Coagulation occurred regularly in less than three minutes. There was no Wassermann.

The urine between 1015 and 1027 in specific gravity showed occasionally a slight trace of albumin; no sugar even after the administration of 100 grams of glucose; no casts; occasionally a few pus and red blood cells.

The subsequent course of the case was not satisfactory. No treatment had any ameliorating effect. There was frequent epistaxis at one period and a prolonged and furious attack of herpes zoster on the right side, acroparesthesia, that caused much discomfort. The headaches, nausea, and vomiting persisted and rendered life miserable. The treatment consisted of various drugs, with no particular result. There were careful applications of the *x*-ray, chiefly over the long bones, which, according to the patient, did much harm, although there was no appreciable change in her condition. Finally I requested Dr. W. S. Newcomet to try radium

over the spleen. This was begun November 14, 1914. Eleven mgr. of radium were used; the entire available stock, in a glass tube, was filtered through lead. Applications were made to the different parts of the spleen for four hours about three times a week until June 8, 1915. They were recommenced October 10, 1915, and continued until February 4, 1916, recommenced March 1, and are still continued. No effect upon the blood count was observed until March, 1915, but since then the count has been distinctly lower, the averages for the two periods being 7,821,000 and 5,674,000. More remarkable was the complete disappearance of the headache, nausea, and vomiting and the return of strength. On November 18 the spleen measures 17 x 17 cm. On February 4 it was 15 x 11 cm. There was repeated epistaxis and return of headache during the summer of 1915 when no radium was used, and nausea and depression in February when it was again temporarily discontinued. Both times there was prompt recovery after the radium exposures were renewed.

Blood Counts.

Date.	Hemoglobin, per cent.	Red blood cells.	White blood cells.
Oct. 30, 1913	115	7,310,000	20,600
Dec. 2, 1913	...	8,040,000	
Dec. 31, 1913	85	6,740,000	19,700
Mar. 13, 1914	114	7,440,000	
May 9, 1914	...	6,220,000	
May 28, 1914	115	8,170,000	
Aug. 21, 1914	125	9,200,000	27,700
Jan. 5, 1915	124	8,040,000	
Feb. 13, 1915	125	9,230,000	
Mar. 24, 1915	112	6,700,000	29,000
June 4, 1915	97	6,910,000	20,700
Aug. 27, 1915	95	5,640,000	29,400
Sept. 15, 1915	92	5,580,000	22,000
Dec. 30, 1915	85	4,860,000	24,000
Feb. 4, 1916	90–100	6,590,000	6,820
Feb. 23, 1916	90	6,120,000	6,750
Mar. 8, 1916	90	5,230,000	
Mar. 21, 1916	80	4,650,000	
April 8, 1916	85	5,060,000	11,200
April 27, 1916	85	5,180,000	9,440
April 14, 1916	90	5,690,000	
June 4, 1916	90	5,640,000	13,440

Differential Count.

Date.	Polynuclears.	Leukocytes.	Mononuclears.	Transitionals.	Mast cells.	Eosinophiles.
Oct. 30, 1913	16,274	1236	1442	1030	618	
Dec. 31, 1913	17,730	..	1182	197	197	197
Feb. 13, 1914	82%	12%	2%	2%	..	2%
Feb. 13, 1915	78%	12%	3%	4%	..	3%
June 4, 1915	16,974	3105	621			
Sept. 27, 1915	26,460	2058	294	294		
Oct. 15, 1915	19,140	1540	660	440		220

DISCUSSION

Dr. Max Einhorn, New York, said with regard to the therapy of polycythemia that he had seen a case of this condition a year ago in a man whose red cells numbered 6,500,000; his principal symptom was dyspnea. He had sought to increase the fluids of the body and so dilute the blood by giving a quart and a half of saline by Murphy drip per rectum daily. The symptoms were much improved by this simple expedient.

REMISSIONS IN LEUKEMIA PRODUCED BY RADIUM IN CASES COMPLETELY RESISTANT TO X-RAY AND BENZOL TREATMENT

By THOMAS ORDWAY, M.D.
ALBANY, N. Y.

Those who have had extensive personal experience with and opportunity for intensive study of leukemia recognize that there have been cases which did not respond to treatment by *x*-rays or benzol. Indeed, following the use of benzol, serious, even fatal, results have been reported, and toxic symptoms also may occur after the use of the *x*-rays. In certain instances benzol may cause a short period of temporary improvement followed by rapid fatal termination.[1] Such termination also may occur with other forms of treatment or without treatment. With the more recent improvements in *x*-ray apparatus by Coolidge and his co-workers, and by perfection in the technic of clinical application, it is probable that the number of cases which are refractory to *x*-ray will be considerably lessened.

Renon, Degrais, and Tournemelle,[2] in an admirable article add a sixth case of leukemia to the five already reported by them. They also refer to the French series of twelve cases of leukemia in which marked improvement resulted from the surface application of radium over the enlarged spleen. Eight of these had already been treated with *x*-rays with no advantage or only with temporary improvement. Pinch, of the Radium Institute of

[1] Graham, C. S., Jour. of the Am. Med. Assn., February 6, 1915, lxiv, 505.

[2] Radiumthérapie de la Leucemia Myéloide. Essai de Comparison entre la Radiumthérapie et la Radiothérapie de Cette Affection, Bulletins et mémoires de la Société médicale des hôpitaux de Paris, 1914, 3. Serie, 37, p. 526.

London,[1] also makes reference to a case of myelogenous leukemia in which the results of radium treatment were excellent. Von Noorden and Falta[2] did not obtain any favorable results in leukemia by the use of radium emanation even by prolonged treatment in the emanatorium. Falta, Kriser, and Zehner,[3] however, produced remissions in leukemia by the injection of thorium X. In the small series of cases reported by them the immediate results were good but the cases had only been followed a very short time so that they did not draw any conclusions regarding end-results of this treatment. German investigators have reported conflicting results from treatment of leukemia by thorium X.

METHODS. *Benzol.* The methods of administering benzol in the treatment of leukemia have now become almost uniform. Capsules, in certain instances coated with salol, containing 0.5 gram of benzol, are given with equal parts of olive oil to diminish the irritating local effect. Two of such capsules are given at first, increasing until ten, that is, 5 grams a day are administered. They should be taken immediately after meals and never during meals, and it is important that the patient should be kept in the hospital during such treatment.[4] It may take ten days to three weeks before the effect upon the blood is observed. It is customary to stop administration when the white count in leukemia has been reduced to 20,000. Boardman states that 16 out of 100 cases fail to show improvement, and that another 8 cases, although reacting favorably at first, died during or soon after the discontinuance of treatment. Also certain toxic effects have been reported, such as gastro-intestinal disturbances, headaches, dizziness, skin eruptions, bronchial and kidney irritation, and hemorrhages. Marked leukopenia with increasing anemia and death may occur.

X-rays. The technic for treating leukemia by the *x*-rays has been very variable, and this may account, to a certain extent, for the variations in the results obtained. Boardman (loc. cit.) states that the *x*-rays have produced improvement in from 20 per cent. to 50 per cent. of the patients, that is, 50 per cent. to 80 per cent. of the

[1] Report of Radium Institute of London, January 1, 1914, to December 31, 1915, p. 33.
[2] Medizinische Klinik, 1911, No. 39. [3] Wiener klin. Wchnschr., 1912, No. 12.
[4] Boardman, W. W., California State Jour. of Med., September, 1915, xiii, No. 9.

cases are refractory. In most cases the long bones as well as the spleen have been radiated. In many instances, however, too little attention has been paid to the principles of cross-fire and filtration (deep therapy). The principle of the so-called "*cross-fire*" is important for the successful application of radium or *x*-rays to large growths or to deeply seated lesions. The method was first described by Domenici and has since been elaborated by others, notably in the treatment of uterine fibroids by *x*-rays in the Freiburg clinic by Kroenig and Gauss. The aim is to concentrate as much of the action of the rays as possible in the deep-seated lesion with the least possible injury to the overlying skin. This may, in certain instances, be accomplished by employing small tubes of radium scattered throughout a tumor mass or by surface applications of heavily screened radium or *x*-rays to a large number of areas on the skin so that each area will not be exposed too long or too intensely. This might be the result in applying the radium to a single area for the time necessary to produce the desired effect on the underlying lesion. By this cross-fire method enormous doses, even 1000 to 1500 Kiemboeck units, may be applied to the deep lesion when not more than 20x could be safely put through one particular surface area. Pfahler uses from 4 to 40 surface areas and passes a full dose through each, making a total of from 80 to 800 units.

To produce any marked effect upon the deeper tissues it is necessary to use screens or filters to check the less penetrating rays which would otherwise be absorbed by the superficial tissues and cause marked destructive changes there before the less numerous and more penetrating rays could act on the deeper tissues. In order to obtain the most penetrating *x*-rays for this method of so-called "deep Roentgen therapy," the well known "Tiefenroentgentherapie" of the Germans, it is necessary to employ a hard tube of high degree of vacuum and an electrical apparatus of high voltage. The rays are not all of equal penetrability and it has been found that they are more homogeneous when the softer have been "filtered out" by an aluminum screen 3 mm. in thickness. Certain roentgenologists also use a heavy piece of leather.

Radium. When radium is used for the treatment, screens or filters of lead 2 or 3 mm. in thickness, of brass 1.2 mm. or other

heavy metal, such as silver, gold, or platinum, allow the penetrating hard beta and gamma rays to pass and intercept the alpha and soft beta rays which would otherwise be absorbed and cause destructive changes in the superficial tissues. As the amount of the more penetrating rays is only a small proportion of the total activity, less than 5 per cent., it is necessary in deep therapy to make exposures correspondingly long.

The principles of cross-fire as well as deep therapy are made use of in the treatment of leukemia by surface applications of radium. The technic of such radium therapy may be illustrated by the striking effect of radium when applied in the proper manner to the surface over the enlarged spleen in cases of myelogenous leukemia. For this the following details have been elaborated:

The area of the enlarged spleen is carefully and plainly marked out with skin pencil or grease paint (of red or black color), the outline being obtained by percussion and palpation. The various landmarks, such as the costal margins, anterior superior spine and crest of the ilia, the symphysis pubis, and the umbilicus are marked. The patient is photographed in an erect position in both front and side views (Figs. 1 and 2). A series of small squares, 3 cm. in diameter, when the radium applicator is 2 cm. in diameter, are marked over the area of the enlarged spleen. It is important not to have the successive application areas too near together or the skin between them will be "burned" by the double dose. The squares thus marked out are numbered serially. A swathe of thin cotton cloth is carefully fitted to the abdomen and the outline of the spleen, bony landmarks and small squares is traced upon it. This swathe must be smoothly and accurately fitted and kept in accurate position by means of the landmarks above mentioned, for it is left in place during each single series of treatments. The purpose of this swathe is to avoid the irritation of repeatedly applying and removing the adhesive plaster which holds the radium applicator in place, for it has been found that the area which is being or has been radiated is particularly sensitive to injury from the repeated application and removing of adhesive plaster. Indeed, such added irritation may induce vesiculation or even superficial ulceration of the skin. Tracings of the areas and landmarks marked on the

swathe are now made on tracing cloth, which serves as a chart for guidance in the following series of treatments. The general method of charting will be seen by the accompanying illustrations (Figs. 3, 4, 5 and 6). This affords a convenient and accurate method of recording the changes in the size of the spleen and in avoiding injury to the overlying skin in the effort to give sufficient radiation to the underlying lesion. With the chart as a guide the radium applicator, screened with 2 or 3 mm. of lead, 15 to 20 thicknesses of filter paper, and wrapped in gauze, is now applied to each of the squares in the order indicated. It is necessary also to add at least as much filtration and protection to the *external* side of the applicator, for the patient may inadvertently rest the arm or leg on the applicator during sleep and a severe burn may thus result. The filter paper is applied to avoid the irritating effect of the secondary rays from the lead, and the gauze adds to the comfort of the patient. If it is desired, the applicator may be rendered even more comfortable by substituting 25 to 30 layers of gauze instead of the filter paper. After from four to six weeks a second series of treatments is usually necessary, the interval between being determined by examinations of the blood and by the local condition of the skin. If the details here described are followed, however, no effect will be produced upon the skin other than very faint pigmentation after several series of radium treatments. The size of the spleen and the bony landmarks should be marked out, a new swathe fitted, and tracings made at each series.

Duration of Application and Amount of Radium Used. When from 50 to 60 mgs. of radium element or millicuries of radium emanation are employed evenly distributed over a surface applicator 2 x 2 cm. in diameter, and the filtration and protection above mentioned is used, the radium may be left in each position from four to six hours; four hours if there are 60 mgs., six hours if there are 50 mgs., and if the filtration is 3 mms. of lead. With this amount of radium and the above technic it is possible for complete remission in leukemia to occur with three series of treatments. Amounts of radium, however, as small as 25 mgs., even when this is in the form of a tube, have reduced the spleen to normal size and have caused the characteristic improvement in the blood and in the general

condition of the patient; but the time required is longer and the series of applications more numerous.

Discussion. In practical radiotherapy, radio-active substances will in certain instances doubtless be preferable to the use of the *x*-rays particularly when there is necessity for the most precise localization, especially within the body or in cavities difficult of access and also when the condition of the patient or circumstances demand portability of the therapeutic agent for convenience or ease of treatment. The disadvantages of radium are its great expense for sufficient dosage in certain cases and also the possibility of loss of the radium salt by accident or theft. The latter may, however, be obviated by the use of emanation, or radio-active gas evolved from a solution of radium; but the expense is thereby increased because of the necessity of retaining a physicist and equipping and carrying on a physical laboratory. When sufficient clinical experience has been gained in the application of the recent advances in the production of highly penetrating homogeneous *x*-rays of great volume by Coolidge and his co-workers, supplemented by careful scientific study of the physiological effects, it is believed that there will be in the majority of cases very little difference in the therapeutic value of the *x*-rays and radio-active substances. With the use of more powerful Roentgen apparatus which is now being elaborated physiological standardization is deemed of utmost importance in order that the best results may be obtained and the danger to patients obviated. It seems possible that similar results to those now produced by radio-active substances may be brought about in a much shorter time by the *x*-rays when the desired quantity and quality of the radiation may be measured in a rational manner so that the results obtained by one man may be compared with those of others, and that there may be a repetition of results from day to day. From the preceding it will be seen that each source of radiation has certain advantages as well as disadvantages. Unless in the near future the cost of production and the selling price of radium is greatly reduced, it would seem with the recent development in the *x*-rays that the latter will become of more general use in the treatment of many diseases.

It has been the practice of many roentgenologists to radiate the

long bones as well as the spleen in cases of myelogenous leukemia. In the writer's experience, however, it has not been necessary or, indeed, seemed advisable, when radium is used as the therapeutic agent, to radiate the long bones. Surface applications of radium over the enlarged spleen in the manner above described produces most remarkable improvement with striking changes in the size of the spleen, the blood picture and the general condition of the patient. In the course of a few weeks, or in certain instances in three or four months, after radium treatment by surface application a spleen which filled almost the entire abdomen and extended well to the right of the median line and into the pelvis (Figs. 1 and 2) and caused marked pressure symptoms has been reduced to normal dimensions so that it was not palpable below the costal margin (Fig. 9). The white cells in the blood were reduced from 500,000 to 6000, the immature forms being especially affected. The hemoglobin increased from 60 or less to 90 per cent. Red blood corpuscles may increase from 2,000,000 to 5,000,000. The abnormal blood cells, myeloblasts, and myelocytes disappear. Indeed, the blood picture returns almost to normal, although some variation in the size of the red cells may persist and there may be relative lymphocytosis. A pale, emaciated, anxious individual, with prominent bony framework, stooping shoulders, and enormously enlarged abdomen, usually loses the anxious expression, becomes plump, the abdomen returns to normal size, the color and strength improve, so that the patient may feel entirely well. The pathological condition, however, sooner or later is apt to relapse, and response is less prompt in subsequent series of radium treatments. Some of the patients treated with radium have been followed for a number of years and kept in good condition by the occasional repeating of radium treatments. Certain cases, however, similarly treated have died of intercurrent infection or have succumbed to the original disease.

Striking changes are found in the urine of patients with myelogenous leukemia treated by radium. There is a marked increase in the total nitrogen, urea nitrogen, and ammonia nitrogen. The uric acid is slightly increased. The total phosphates are increased remarkably. There is apparently no accumulation of uric acid in

the blood, at least when the kidneys are in normal condition. Because of this marked increase in the metabolism it seems advisable to have the patient on a purin-free diet during and following the series of radium treatments. The changes in the metabolism of patients treated by radium resemble in certain respects those resulting from treatment by *x*-rays.

From the clinical point of view there is particular interest in the effect of radium upon cases which have proved completely refractory to *x*-ray and benzol treatment, and of these the following record is an example.

Illustrative Case. The patient, Mrs. A., aged thirty years, first consulted her physician April 11, 1915, for an obstinate, hacking, unproductive cough which had at that time persisted for about a month. The cough was somewhat spasmodic, so much so that whooping-cough had had been suspected. She stated that she had also had "inflammation of the eyes," which had been treated by an oculist for three days with ice compresses. On April 11 general examination by the patient's physician disclosed a greatly enlarged spleen, and a blood examination two days later was as follows:

Red blood cells, 3,750,000.
White blood cells, 280,000.
Hemoglobin, Sahli, 62 per cent.
Polymorphonuclear leukocytes, 53 per cent.
Lymphocytes, 4 per cent.
Eosinophiles, 2 per cent.
Large mononuclears, 2 per cent.
Myelocytes, 39 per cent.

The cough became so troublesome that it interfered with the patient's sleep and the uvula was incised by a laryngologist without effect in the hope that it might improve the symptom. The patient was given sodium cacodylate, grains $\frac{3}{4}$, subcutaneously twice a week from April until July but there was no improvement. The cough continued and the abdomen constantly grew larger. From April to June the waist increased 3 inches in circumference and the abdomen continued to increase until the first week in November, 1915; the patient stated that the enlargement and pressure sensations corresponded with those of pregnancy at eight months (Figs. 1 and 2). The increasing pressure caused great annoyance from the lessened control of the bladder due to an old laceration at childbirth. Not only did the troublesome cough persist, but the patient became more and more short of breath and perspired freely. The perspiration was most noticeable in the legs. During the latter part of the summer and the early

fall the perspiration was so marked the sheets were wet and the weakness much increased. In the early part of July the sodium cacodylate was stopped, and on July 15 *x*-ray treatment was begun and continued every other day until September 13. On September 18 the patient went to Baltimore, where she was seen in consultation with Dr. Louis Hamman, who on September 23 sent to the patient's physician the following report:

"Mrs. A. came to Baltimore for an examination and through Dr. H. H. Young was referred to me. I am sure that I will add nothing new in what I have to say; but I was anxious to have the opportunity to report to you the results of the examination.

The general physical examination shows nothing abnormal except the palor of the skin, and a tremendously enlarged spleen. The spleen reaches well beyond the middle line and below descends into the pelvis. The blood shows:

Hemoglobin, 58 per cent.
Red blood corpuscles, 2,912,000.
White blood corpuscles, 460,000.

The hemoglobin reading may be a little too high since the 'muddiness' of the blood makes an exact reading difficult. A differential count of 500 cells gave the following proportion:

Polymorphonuclear neutrophiles, 58.2 per cent.
Polymorphonuclear eosinophiles, 2 per cent.
Polymorphonuclear basophiles, 2.6 per cent.
Neutrophile myelocytes, 31.6 per cent.
Eosinophiles, 1.2 per cent.
Lymphocytes, 1.4 per cent.
Large mononuclear cells (including myeloblasts), 3 per cent.

In counting 500 cells, 2 normoblasts and 1 intermediate form of nucleated red cell were seen.

Mrs. A's condition, therefore, is typical of the chronic form of myeloid leukemia.

Mrs. A states that she has been treated with the *x*-rays, and that she has had injections, which I presume were injections of some form of arsenic. Apparently little improvement has followed the treatment, since the blood, according to her statements, has remained practically stationary. This being so, I think it is very important, while Mrs. A's general condition is still good, that treatment be undertaken more radically. The things that I would propose are these:

First—I think that she should be absolutely in bed, if possible, out of doors. Since it would be difficult for her to be in bed at home and receive the proper *x*-ray treatments, she would be much better off in a hospital. Of course the diet should receive appropriate attention.

Second—The *x*-ray treatment should be continued. The exact method of application must be left to one experienced in *x*-ray work; but I think it should be pushed energetically.

Third—I should advise a thorough and energetic course of benzol treatment.

I outlined this plan to Mrs. A, and she was somewhat undecided whether she would enter the Johns Hopkins Hospital for treatment, or whether she would return and enter the hospital at Albany. I told her that I would write you fully about my examination and that it would be best for her to leave the decision, whether she should remain at home or should come to Baltimore for treatment, entirely in your hands. This she has decided to do, and will consult you as soon as she returns home."

On October 1 the patient entered the Albany Hospital and *x*-ray treatment was continued without any effect until October 25. In all, 37 areas were exposed, including practically all the long bones and the area of the enlarged spleen. Dr. Howard had immediate charge of the *x*-ray applications under the supervision of Dr. John M. Berry, roentgenologist to the Albany Hospital. The technic was as follows:

Spark gap varied from 6 to 8 inches, filter 3 mm. of aluminum, tube distance 10 to 11 inches, current 5 to 8 m.a., and the time of each exposure varied from five to ten minutes.

Over the spleen a cone 1 inch in diameter was used, over the long bones one 3 inches in diameter. On October 25, through the courtesy of Dr. T. F. Doescher, the patient's attending physician, I had the opportunity of studying the case. I would also express my thanks to Dr. Doescher for the large number of blood examinations made by him. At this time the patient was sitting comfortably in bed, skin and mucous membranes were somewhat pale, and the breathing slightly rapid and shallow. The bony framework of the chest was prominent (Fig. 1). The left border of cardiac dulness was 14.5 cm. to the left of the median line, the right border 2 cm. to the right of the median line. The upper border was in the second space. The first sound at the apex was rather short and somewhat resembled the second. There were no murmurs. The lungs showed normal resonance and respiration throughout except at the right base posteriorly where, extending midway to the angle of the scapula, there was moderate dulness and a few fine moist rales. The upper border of the liver dulness anteriorly was at the fourth space, the lower border 2 cm. below the costal margin. The abdomen was enormously distended and about the size of pregnancy at eight months. A large mass, apparently the spleen, filled almost the entire abdomen except the right upper quadrant. In the left midaxillary line the upper border of splenic dulness was at the seventh rib. The right border of the spleen on the level with the umbilicus was 7.5 cm. to the right of the median line, and on a level with the anterior superior spine the right border was 8 cm. to the right of the median line. The splenic notch was distinctly felt. Anteriorly the mass could be felt extending into the pelvis (Figs. 1, 2 and 3). Extremities: the reflexes were normal; no

edema. Glands: there was no general superficial glandular enlargement. A radiograph of the chest made by Dr. John M. Berry showed general haziness of the lungs and a faint shadow at the right base, apparently due to thickened pleura.

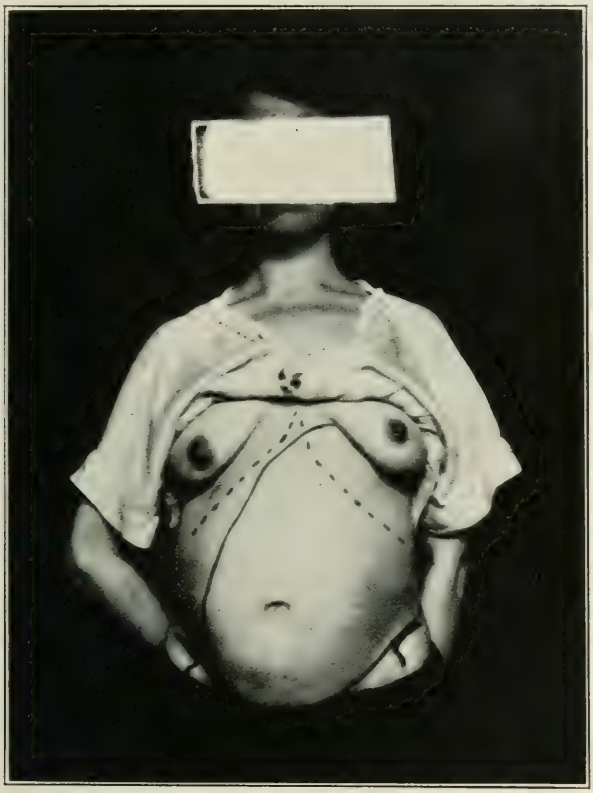

FIG. 1.—Photograph of patient November 5, 1915, showing the outline of the enormously enlarged spleen and the prominence of the bony framework. The costal margins, crests and anterior superior spines of the ilia are also outlined. (Front view.)

Past History. Patient had whooping-cough when eight years old, measles at nine, and pneumonia with pleurisy at thirteen. When three years old she had chronic conjunctivitis, and has worn glasses for years She has two children, six and two years old. Both are well. She has had no miscarriages. Average weight has been 155 pounds.

Family History. Father died of Bright's disease at fifty-seven; mother alive and well. One sister died of spinal meningitis, two brothers alive and well.

Radium Treatment. At a consultation of Dr. Arthur W. Elting, Dr. T. F. Doescher, and Dr. Thomas Ordway with the patient's husband the advisability of radium treatment was thoroughly discussed and it was

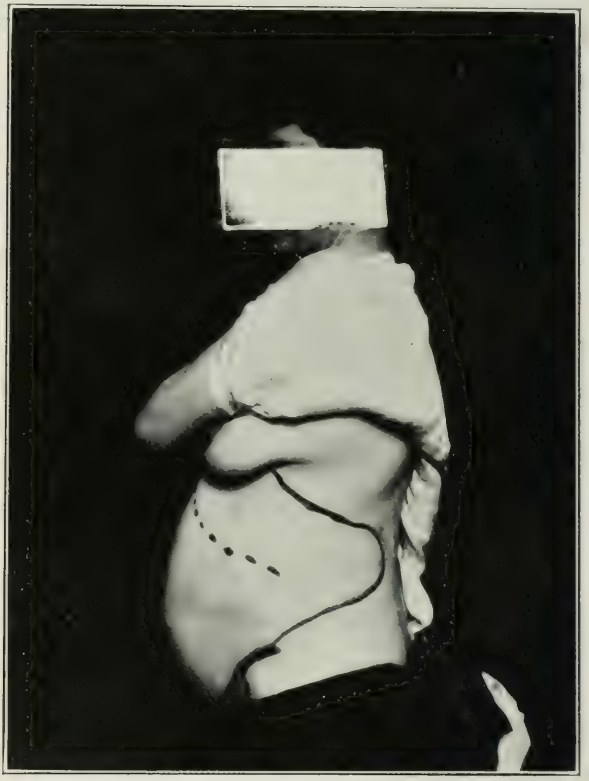

FIG. 2.—Same as Fig. 1, November 5, 1915. (Side view.)

explained to her husband that, notwithstanding the fact that the former methods of treatment, including arsenic, *x*-rays and benzol had not produced any improvement, it was possible that radium treatment by surface application over the spleen might induce a remission. It was carefully explained, however, as probable that even if the general condition improved and the spleen became reduced in size to approximately normal, the condition would merely be regarded as a remission and not in any sense

as a cure. It was suggested that if such a great reduction in the size of the spleen and improvement in the general condition of the patient occurred splenectomy might then be considered. Owing to the courtesy and coöperation of Drs. James Ewing and R. S. Bosworth of the General Memorial Hospital in New York City, radium emanation was obtained for treatment.

Radium Treatment, Series I. November 6, 1915, 6 P.M., 49.5 millicuries of radium emanation in square applicator 2 cm. by 2 cm. was applied to the abdomen to area No. 1 (Fig. 3) for four hours. It was applied successively to the consecutive areas for a similar time. The filtration used was 1 mm.

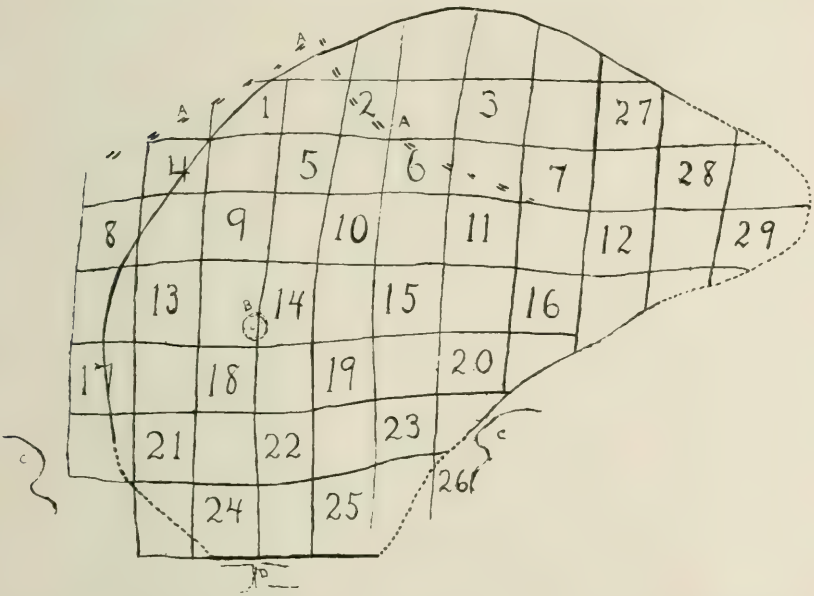

FIG. 3.—Tracing November 5, 1915, indicating the areas over the enlarged spleen exposed in the *first* series of radium treatments. The costal margins, umbilicus, crests and spines of the ilia and symphysis pubis are also indicated.

of silver, 1 mm. of lead, 20 sheets of ordinary filter paper, 10 layers of gauze applied by adhesive plaster to a fitted swathe of cotton cloth. When 22 squares had been covered in the manner above described the strength of the radium was approximately 25 millicuries. November 22 the general condition of the patient was good, the spleen somewhat smaller, and the abdomen was distinctly softer.

Radium Treatment, Series II. December 18, 1915, 60 millicuries of radium emanation were applied to the surface over the area of enlarged spleen (Fig. 4), using the same technic as in series Number 1, except that 3 mm. of lead were used for filtration and the radium was left for six hours

on each of the areas indicated on the chart. On this date the spleen was very much smaller, the general condition of the patient was excellent as to

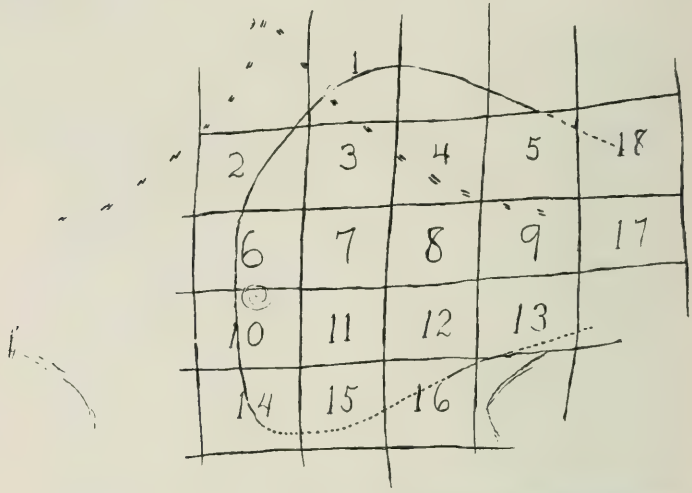

FIG. 4.—Tracing December 18, 1915, showing the areas exposed in the *second* series of radium treatments and the marked reduction in the size of the spleen.

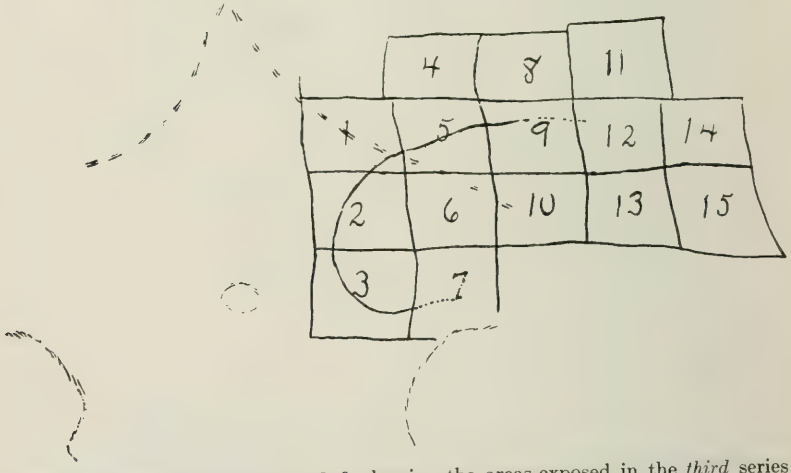

FIG. 5.—Tracing January 27, 1916, showing the areas exposed in the *third* series of radium treatments and the marked reduction in the size of the spleen.

strength and color, and the troublesome cough had entirely disappeared. The second series of radium treatments was ended December 22.

Radium Treatment, Series III. January 27, 1916, applications were started at 7 P.M. The applicator contained 61 millicuries of radium emanation at 12.15 P.M. of this same date. The spleen is very much smaller and occupies only the left upper quadrant (Fig. 5). The radium was applied to each square as indicated on chart for six hours; 3 mm. of lead were used for filtration and the same amount of paper and gauze as in Series I.

January 31, 1916. Third series of radium treatments concluded. Gross photographs (Figs. 7 and 8) show the improved nutrition of the patient and marked diminution in size of the splenic area. Patient's weight, 143 pounds. Corrected weight, deducting 5 pounds for clothing, 138 pounds. White blood count, 28,000. General condition excellent.

FIG. 6.—Tracing April 15, 1916, showing the marked reduction in the size of the spleen which cannot be felt below the costal margin. The costal margins, the umbilicus, the ilia and the symphysis pubis are also indicated.

February 26, 1916. White count, 13,000. General condition excellent.

April 15, 1916. Photographs taken (Figs. 9 and 10) showing greatly improved nutrition and general condition of the patient and marked reduction in the size of the splenic area (Fig. 6). Spleen is no longer palpable below the costal margin. Weight $156\frac{1}{4}$ pounds; corrected, for clothes, $151\frac{1}{4}$ pounds. Patient has gained $13\frac{1}{4}$ pounds in weight since January 31, 1916, notwithstanding the great reduction in the size of the spleen. The muscles are firm, color and strength are good, sleep, appetite, and general condition are excellent. The cough, which had been exceedingly troublesome, and had not responded to local or general treatment, entirely disappeared a short time after the first series of radium treatments.

and has not returned. The catamenia, which was regular every five weeks before September, was scanty on September 5, then it did not occur until November 25, after which it was regular every three or three and a half weeks.

Except for slight variation in size and shape of the red cells the blood examination was practically normal. The red blood cells, 4,800,000;

FIG. 7.—Photograph of the patient January 31, 1916, showing the improved nutrition and the marked reduction in the size of the spleen. (Compare with Fig. 1, front view.)

white blood cells, 5800; the hemoglobin, 90 per cent.; the polymorphonuclear leukocytes, relative number, 50.3 per cent.; absolute number, 2917; lymphocytes, relative number, 45.7 per cent.; absolute number, 2650; myelocytes, none; eosinophils, relative number, 0.3 per cent.; large mononuclears, relative number, 3.1 per cent.; mass cells, relative number, 0.6 per cent.; number of cells counted, 322. No blasts seen.

May 15, 1916. General condition of the patient has continued to remain excellent and she has been about actively and attended to her usual duties. As she has been upon her feet much more, owing to her improved general condition, the frequency of micturition, from lessened control of the bladder due to an old laceration at childbirth, caused considerable annoyance, so that she entered the Albany Hospital on May 3, 1916, and was

FIG. 8.—Same as Fig. 7, January 31, 1916. (Side view.)

operated upon by Dr. John A. Sampson. The possible danger of general anesthetic was thoroughly discussed and gas and oxygen were used instead of ether because they seemed safer. Patient had considerable postoperative pain, but the wound of the pelvic repair operation healed normally.

On May 15 the white cells were 8000 and the red cells 4,600,000.

June 15, 1916. The pain resulting from the operation, mentioned under last note, is relieved, but the patient is bothered with neuralgia, apparently

due to the teeth. White count, 6040; red count, 4,580,000; hemoglobin, 90 per cent.

June 27, 1916. Owing to the persistent neuralgia the patient's dentist, Dr. Le Roy S. Blatner, was consulted, and on June 25 he found the condition to be due, apparently, to a crowned tooth which had broken and the nerve exposed. As he was not able to secure satisfactory anesthesia by

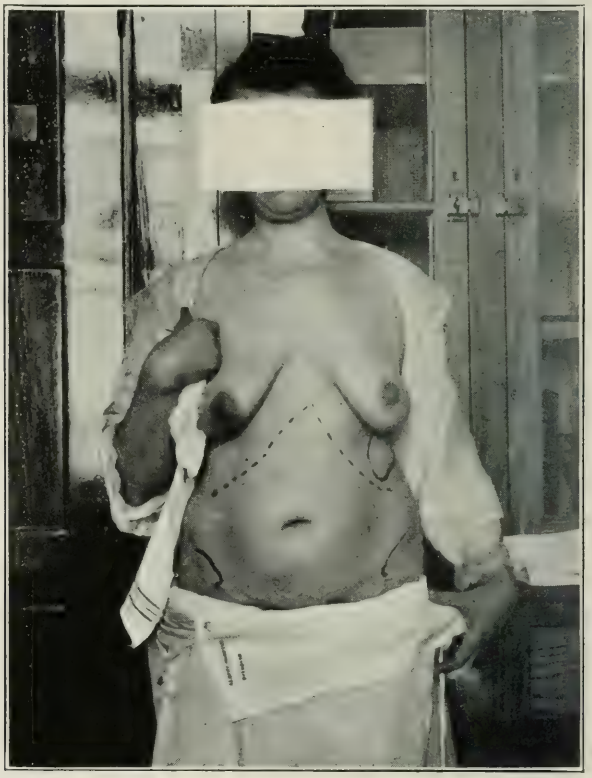

FIG. 9.—Photograph of patient April 15, 1916, showing greatly improved nutrition and indicating the marked reduction in the size of the spleen which was not palpable below the costal margin.

such local measures as cocain or arsenic, the patient was given oxygen and nitrous oxide anesthesia and the nerve removed. The tooth was not extracted. After this the pain was relieved. There was, however, some oozing of blood between the tooth and the gum, and on June 27, when the patient was seen by the writer, there was oozing from the gum in this region and elsewhere to a slight extent. There were also numerous minute

hemorrhagic puncta in groups scattered over the skin of the body, particularly in the lower part of the legs. The general condition of the patient, however, was excellent. She had been up and about until this time, when she was put to bed. The spleen, which previously had not been palpable, was now distinctly felt 7 cm. below the costal margin, and extended almost to the median line. On pricking the lobe of the ear to make a blood count

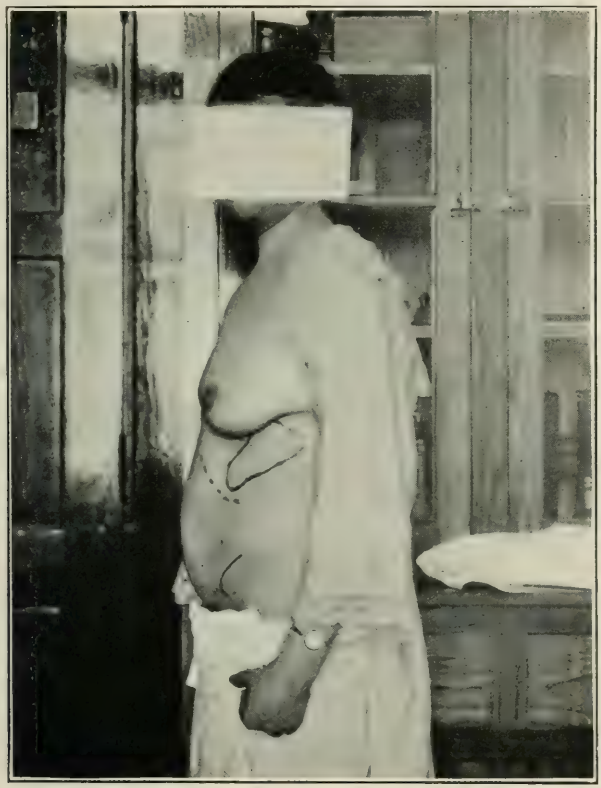

FIG. 10.—Same as Fig. 9, April 15, 1916. (Side view.)

the blood was a peculiar dark color and of watery consistency; it showed little tendency to clot. The white count was 24,600 and the red count 3,770,000. Urine: specific gravity, 1.025; trace of albumin; few casts and polymorphonuclear leukocytes. Although the patient still felt perfectly well, and the general condition was good, it seemed probable that there was a sudden recurrence of the condition of the so-called hemorrhagic type of termination. Notwithstanding the probability that another series of

radium treatment would avail little in such a crisis, the patient was admitted to the Albany Hospital on July 1 and the fourth series of radium treatments was given by Dr. T. F. Doescher with the same technic as in previous series. The bleeding from the gums had become general; there had been an abundant hemorrhage from the nose which was only controlled by packing. The skin was covered with numerous ecchymoses, discrete, and in "blotchy" areas. There was continuous discharge of blood from the uterus. Bleeding continued in spite of the administration of horse serum. On July 4 the patient complained of a very severe headache, which was different from headaches to which she had been subject for years. She finally fell asleep and could not be aroused; she had numerous generalized convulsions, the pulse became weaker, and the patient died on July 5.

Blood Examination. *Comparison of Total Number of White Cells and Red Cells and of the Percentage of Hemoglobin before, during, and following Treatment.* From April to June, 1915, the white cells varied from about 300,000 to 450,000, the red cells from 3,800,000 to 3,600,000, and the hemoglobin remained about 60 per cent. During this time, therefore, the sodium cacodylate treatment above referred to produced no marked effect.

From July to November, 1915, the white cells increased to 500,000, the red cells for a few weeks gradually increased to 3,900,000 and then decreased markedly during August and September to 2,200,000, and the hemoglobin diminished to 50 per cent. During the early part of this period the *x*-rays were begun, and later, because there was no apparent beneficial influence from the *x*-rays, it was combined with benzol treatment. Shortly after the use of benzol the marked reduction in the red cells and the hemoglobin above mentioned occurred, while the number of white cells was not diminished. Because of this and from the fact that there were definite toxic symptoms (see above), benzol treatment was omitted, and although *x*-rays were continued for a short time, there was no apparent change in the white cells or hemoglobin. The first series of radium treatment was followed by a fall in the white cells from 495,000 to 159,000, a rise in the red cells from 2,790,000 to 3,620,000, and the hemoglobin from 50 per cent. to 76 per cent. After the second series of radium treatments the white cells fell to 74,000, the red cells and hemoglobin rose to 4,020,000 and 81 per cent. respectively. After the third series of radium treatments the white cells fell to 5800, the hemoglobin rose to 90 per cent., and the red cells to 4,800,000. The blood, numerically, remained normal for somewhat over three months, when there was a sudden, rapid increase in the size of the spleen, multiple hemorrhages in the skin and mucous membranes, and the white count rose to 24,600, and the red cells decreased to 3,770,000. The record of the number of red and white cells and the percentage of hemoglobin is shown in tabular form in Fig. 11 and charted in Fig. 12.

Date.	Red cells.	White cells.	Hemoglobin.
April 13, 1915	3,750,000	280,000	62
20, 1915	3,680,000	286,000	60
May 1, 1915	3,650,000	290,000	60
20, 1915	3,600,000	292,000	60
30, 1915	3,620,000	310,000	59
June 10, 1915	3,640,000	360,000	61
22, 1915	3,560,000	392,000	60
July 1, 1915	3,680,000	440,000	60
8, 1915	3,690,000	480,000	60
27, 1915	3,890,000	431,000	62
Aug. 4, 1915	3,320,000	442,000	61
19, 1915	3,180,000	462,000	59
Sept. 10, 1915	3,090,000	460,000	58
23, 1915	2,912,000	460,000	58
30, 1915	2,850,000	450,000	58
Oct. 11, 1915	2,510,000	432,000	54
25, 1915	2,230,000	496,000	50
Nov. 2, 1915	2,750,000	470,000	50
3, 1915	2,800,000	467,000	49
4, 1915	2,810,000	445,000	50
6, 1915	2,790,000	495,000	50
9, 1915	2,930,000	446,000	50
13, 1915	2,910,000	430,000	51
16, 1915	3,090,000	406,000	54
18, 1915	2,900,000	325,000	52
20, 1915	2,980,000	264,000	54
23, 1915	3,180,000	258,000	55
27, 1915	3,020,000	256,000	59
30, 1915	3,370,000	220,000	68
Dec. 3, 1915	3,800,000	286,000	72
6, 1915	3,750,000	282,000	70
10, 1915	3,680,000	332,000	69
15, 1915	3,300,000	274,000	69
19, 1915	3,620,000	159,000	76
21, 1915	3,640,000	158,000	74
24, 1915	3,700,000	110,000	74
28, 1915	3,720,000	72,000	75
31, 1915	3,740,000	73,600	75
Jan. 14, 1916	3,760,000	74,000	75
14, 1916	3,900,000	63,000	78
21, 1916	3,880,000	75,000	78
28, 1916	4,020,000	74,000	81
31, 1916	4,120,000	28,000	84
Feb. 5, 1916	4,090,000	17,600	83
8, 1916	4,100,000	17,800	84
11, 1916	4,180,000	14,920	85
16, 1916	4,240,000	13,800	87
22, 1916	4,380,000	14,400	88
Mar 1, 1916	4,670,000	13,000	89
27, 1916	4,660,000	7,200	89
April 15, 1916	4,800,000	5,800	90
May 15, 1916	4,600,000	8,000	
June 15, 1916	4,580,000	6,040	90
June 27, 1916	3,770,000	24,600	

FIG. 11.—Table showing the total number of red and white blood cells and the percentage of hemoglobin.

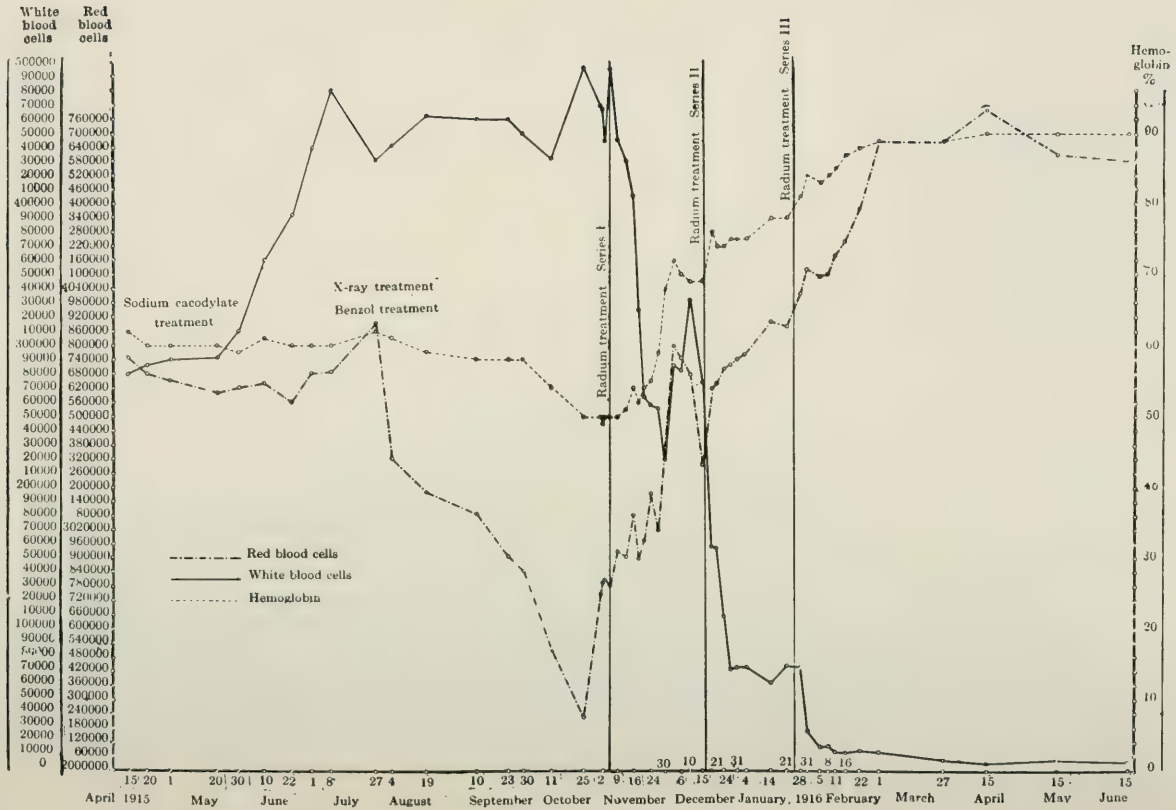

FIG. 12.—Chart showing the total number of red and white cells and the percentage of hemoglobin.

Comparison of the Relative and Absolute Number of White Blood Cells. Blood smears were stained by both Wright's and Giemsa stain. In making the differential counts the following simplified classification was adopted for the purpose of clearness.

Myelocyte. The term myelocyte was used to include typical myelocytes with characteristic granules. The larger, non-granular myeloblasts, many of which morphologically it is difficult to distinguish from the large mononuclear leukocytes, and cells transitional between these two forms or premyelocytes, were included under the general term myelocytes. Neutrophilic, basophilic, and eosinophilic myelocytes were not counted separately.

Polymorphonuclear Leukocytes. With the polymorphonuclear leukocytes were also included the immature forms, some with granules and occasionally bilobed nuclei, the so-called metamyelocytes.

Eosinophile. Under the heading eosinophiles, slightly immature forms were considered.

Lymphocyte. No differentiation between large and small lymphocytes was made.

During the early months of the study of this case no attempt was made to differentiate morphologically between certain myeloblasts and large mononuclear leukocytes. Indeed, this would seem very difficult even with the aid of the oxidase reaction. In the latter part of the study, however, when all the myelocytes had disappeared following treatment, the term "large mononuclear leukocyte" was used. The so-called transitional and endothelial cells have been regarded as synonymous with large mononuclear leukocyte.

Mast Cells. Only typical mast cells were included under this term.

Blasts. While making the differential counts an attempt was made to distinguish normoblasts, the intermediate forms, and megaloblasts.

Following the radium treatment above described the relative number of polymorphonuclear leukocytes increased from about 60 per cent. to 78 per cent., and then diminished to 50 per cent., whereas the absolute number fell from 299,475 to 2917. The relative number of lymphocytes rose from 2.3 per cent. to 45.7 per cent. The absolute number of lymphocytes fell from 11,750 to 2650. The relative number of myelocytes fell from 36 per cent. to zero and the absolute number of myelocytes fell from 178,200 to zero. There was little change in eosinophiles, the relative number diminishing from 1.2 per cent. to 0.3 per cent. The increase in the large mononuclear leukocytes from zero to 3.1 per cent. is in part only apparent for the reasons above described. Mast cells increased from zero to 4.3 per cent. and later diminished to 0.6 per cent. The blasts, which were present as normoblasts, intermediate forms, and megaloblasts, from 3 to 6 in counting between 500 and 600 cells, entirely disappeared. The records of the comparison of the relative and absolute number of white cells are tabulated in Fig. 13 and charted in Fig. 14.

Date.	Polymorphonuclears.		Lymphocytes.		Myelocytes.		Eosinophiles, relative.	Large mononuclears, relative.	Mast cells, relative.	No. cells counted.	No. blastomycetes seen.
	Relative.	Absolute.	Relative.	Absolute.	Relative.	Absolute.					
April 13, 1915	55.6	155,680	2.4	6,720	40.1	112,280	1.9	0.0	0.0	636	7–1–0
July 26, 1915	60.1	259,391	1.7	7,337	36.1	155,807	2.1	0.0	0.0	664	4–0–2
Sept. 23, 1915	60.8	279,680	1.4	6,440	35.8	164,680	2.0	0.0	0.0	500	2–1–0
Nov. 2, 1915	59.4	279,180	2.5	11,750	36.5	171,550	1.6	0.0	0.0	636	2–0–1
Nov. 6, 1915	60.5	299,475	2.3	11,385	36.0	178,200	1.2	0.0	0.0	795	4–1–0
Nov. 9, 1915	62.2	277,412	3.7	16,502	33.4	148,964	0.7	0.0	0.0	539	2–1–0
Nov. 13, 1915	67.2	274,960	1.8	7,740	29.5	126,850	1.1	0.3	0.1	669	0–0–0
Nov. 16, 1915	57.5	233,450	2.9	11,774	38.3	155,498	1.3	0.0	0.0	611	6–0–1
Nov. 23, 1915	62.9	162,282	2.4	6,192	28.0	72,240	2.4	0.0	4.3	332	4–0–0
Dec. 3, 1915	73.2	209,352	2.5	7,150	21.5	61,490	1.0	0.7	1.1	719	3–0–0
Dec. 20, 1915	65.3	103,827	4.6	7,314	28.0	44,520	1.1	0.0	1.0	694	3–0–2
Jan. 4, 1916	64.3	47,582	17.4	12,876	12.5	9,250	1.0	1.7	3.1	478	0
Feb. 5, 1916	78.6	13,833	15.2	2,675	1.3	982	0.1	4.6	0.2	785	0
Mar. 7, 1916	65.6	8,528	29.6	3,848	0.3	39	0.7	3.8	0.0	287	0
Mar. 27, 1916	51.4	3,700	44.7	3,218	0.0	0	1.2	2.6	0.1	535	0
April 15, 1916	50.3	2,917	45.7	2,650	0.0	0	0.3	3.1	0.6	322	0

FIG. 13.—Table showing comparison of the relative and absolute number of white cells.

Morphological Appearance. Blood smears at the beginning of radium treatment were typical of myelogenous leukæmia (Fig. 15), showing large numbers of myeloblasts and myelocytes. The white count was 495,000, the polymorphonuclear leukocytes relative number 60.5 per cent., absolute number 299,475, myelocytes relative number was 36 per cent., absolute number 178,200.

During radium treatment the myelocytes diminished rapidly, the blood smears showing an apparent increase in polymorphonuclear leukocytes and a marked diminution in myelocytes (Fig. 16). The total white count was 159,000, the relative number of polymorphonuclear leukocytes 65.3 per cent., and the absolute number was 103,827. Relative number of myelocytes was 28 per cent., and the absolute number 44,520.

Following the three series of radium treatments the relative and absolute numbers of white and red cells and the percentage of hemoglobin were normal, and all abnormal white cells had disappeared. The red cells, however, even at the height of the patient's improvement, continued to show considerable variation in size and shape (Fig. 17).

Uric Acid in the Blood. Chemical examination of the blood obtained on November 5, 1915, the day before the radium treatment, showed 3.78 mg. per 100 c.c. of blood. Similar examination made of blood obtained November 27, 1915, three weeks after the treatment by radium had been commenced, showed 2.48 mg. per 100 c.c. of blood. A third examination of blood obtained on March 3, 1916, about five weeks after radium treatment had been concluded, showed 3.5 mg. of uric acid per 100 c.c. of blood. From the above it is evident that there is little change in the uric acid in

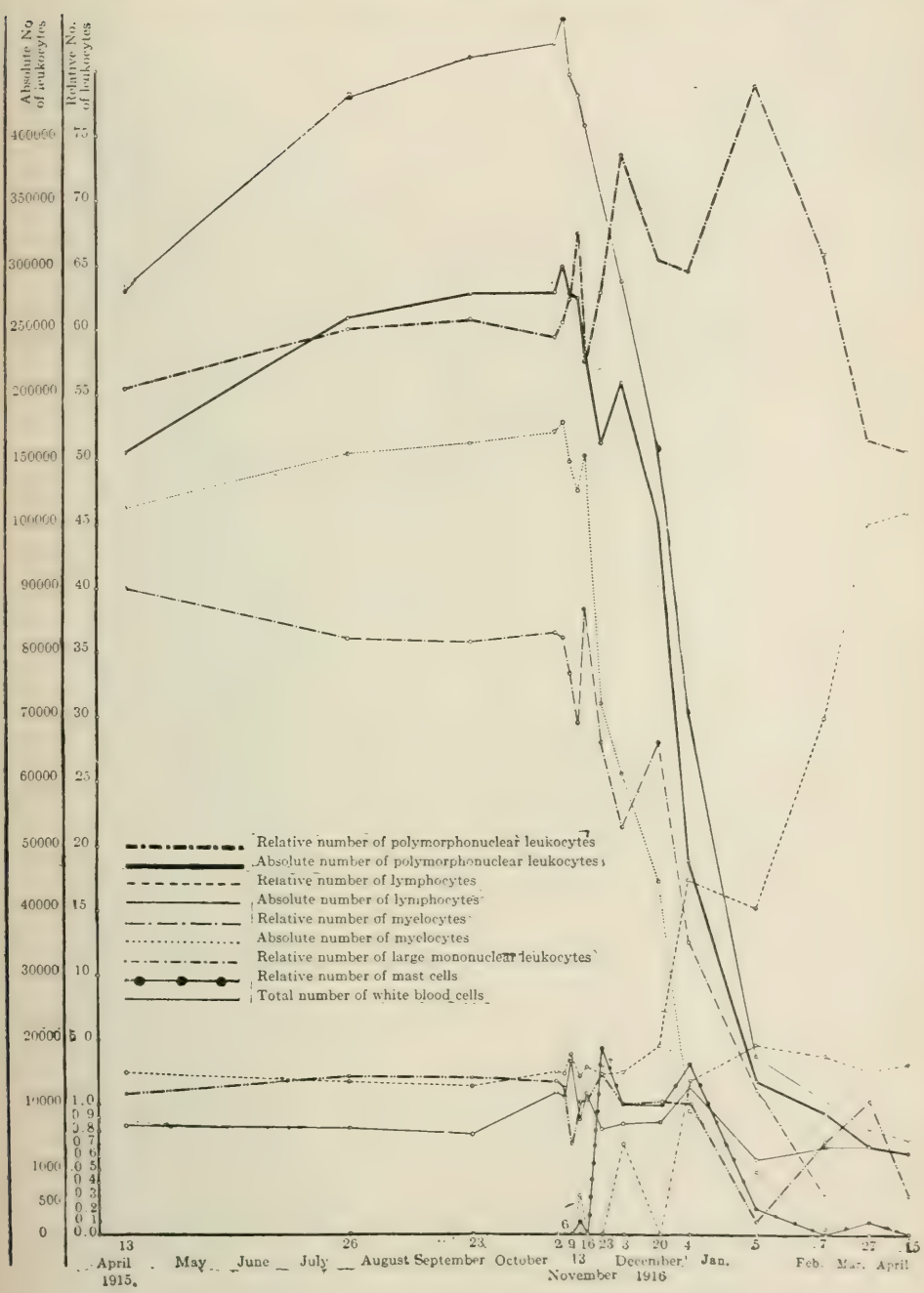

FIG. 14.—Chart showing comparison of the relative and absolute number of white blood cells.

the blood compared with the increase in the uric acid in the urine. (See below.)

Chemical Examination of the Urine.[1] Patient was put on a purin-free diet before, during, and for considerable periods after each series of radium treatment. After the first series of radium treatment the total nitrogen, urea nitrogen, and ammonia nitrogen excretion began to increase immediately and at the end of seven days the excretion reached a maximum and was more than double. After the seventh day there was slight decrease

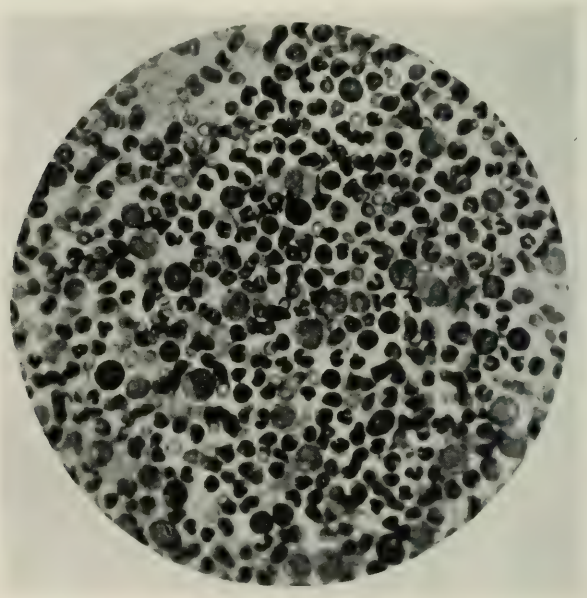

FIG. 15.—Photomicrograph of blood smear November 6, 1915, showing large numbers of myeloblasts and myelocytes. The white count was 495,000; the polymorphonuclear leukocytes, relative number, 60.5 per cent.; absolute, 299,475; myelocytes, relative number, was 36 per cent.; and the absolute number, 178,200.

and then remained more or less constant. The uric acid output showed a slight increase for the first seven days and then remained about the same with several wide variations. The elimination of total phosphates showed a most remarkable result. The phosphates increased immediately after

[1] I am indebted to Dr. Arthur Knudson, Professor of Biological Chemistry, Albany Medical College, under whose direction the chemical examination of the urine was made in association with Mr. Theodore Erdos. A detailed report of the urine examination will be the subject of a separate article by Prof. Knudson and Mr. Erdos.

the first day of treatment. At the end of the seventh day the excretion had been triple. There was then a gradual fall until the next series of radium treatments. The fall in excretion of phosphates did not reach normal but remained about twice normal.

After the second series of radium treatments the total nitrogen, urea nitrogen, ammonia nitrogen, and uric acid showed a similar increase in excretion for six or seven days. The phosphate excretion likewise increased.

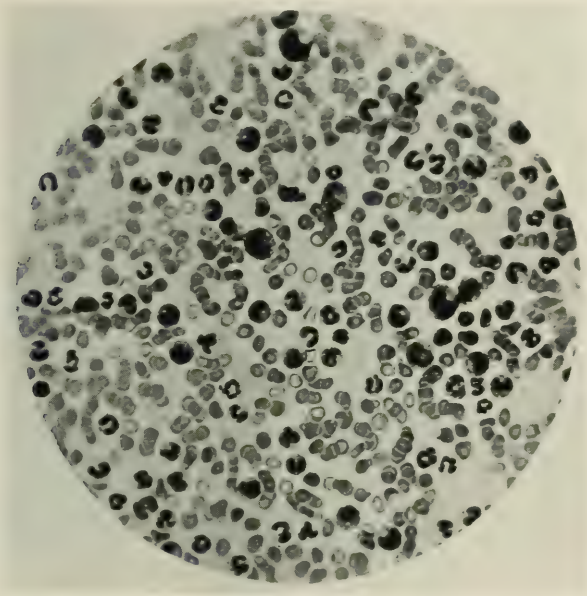

FIG. 16.—Photomicrograph of blood smear December 20, 1915, showing apparent increase in polymorphonuclear leukocytes and the marked diminution in myelocytes. The total white count was 159,000, relative number of polymorphonuclear leukocytes 65.3 per cent., and the absolute number 103,827. Relative number of myelocytes was 28 per cent., and the absolute number 44,520.

After the third series of radium treatments the increased excretion of the various substances above mentioned was similar. It is interesting to note that after all three series of radium treatments the increase in excretion continued for about six or seven days after the beginning of treatment and then dropped. The phosphate elimination showed the greatest increase.

SUMMARY. Results similar to those above described in the treatment of leukemia have been reported by various observers who have used the *x*-rays for treatment, particularly when similar methods

were used and the applications made over the enlarged spleen. In the majority of cases, however, the long bones have also been rayed. It is to be noted that in the surface applications of radium the results were obtained without radiating the long bones, in fact, in a case in which the long bones were radiated there was apparently an increase rather than a diminution in the white cells. It is also believed that the results are more prompt by the radium treatment

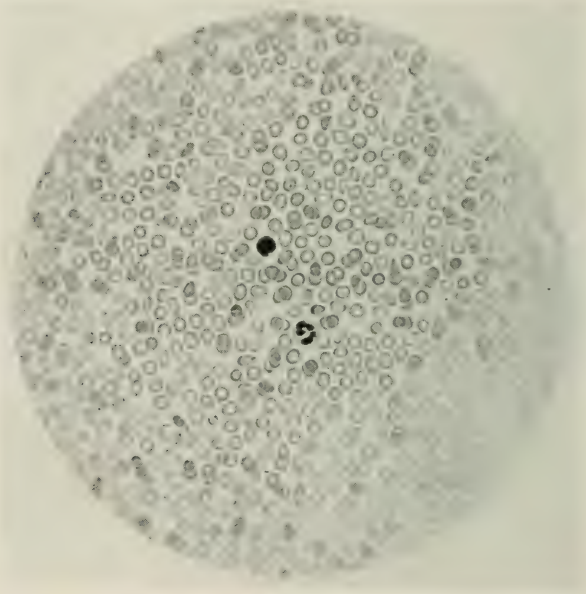

FIG. 17.—Photomicrograph of blood smear March 27, 1916. Total number of white cells 7200; relative number of polymorphonuclear leukocytes 51.4 per cent., absolute number 3700; myelocytes, relative number, none; absolute number, none. Red cells show considerable variation in size and shape.

than by the *x*-rays as usually employed, and no case has been accompanied by toxic symptoms, although there is a marked increase in the endogenous purin metabolism. On a purin-free diet, uric acid, urea, total nitrogen, phosphates, and acidity of the urine are remarkably increased by radiation. Because of this it is advisable to have a careful examination of the urine before treatment is begun and to place the patient during and after-treatment on a purin-free

diet. The recent developments in the *x*-rays by Coolidge and his co-workers and the resulting accurate standardization of the dosage, and the increased intensity and penetrating power make it probable that the results of *x*-ray treatment will be equally as good as those obtained by radium.

Sixty milligrams of radium element or millicuries of emanation used by the technic above described would seem most satisfactory; 25 mg. of radium element, however, have produced similar results, although the number of applications was greater and the response much more gradual. In the case above detailed only three series of applications were necessary before the blood returned to normal. In other instances with less perfected technic six or more series have frequently been necessary.

Many of the cases which responded promptly to radium applications over the spleen had previously proved refractory to *x*-ray and benzol treatment. Although the results in the radium treatment of leukemia are most striking in the chronic myelogenous variety in certain cases of lymphatic leukemia, the effects are almost equally as good. In the acute, fulminating leukemias radium treatment is of no value. In some cases of chronic myelogenous leukemia, however, even when the general condition is very poor at the start, there may be marked temporary improvement. It must be understood, however, that the results should be regarded at the present time merely in the light of palliation and not as a cure. It is hoped, however, that future research will at least increase the duration of these remissions. It is suggested that the spleen be removed during the period of most marked improvement, at the height of a remission when the spleen is of normal size and the general condition of the patient excellent. Although the treatment must not be considered at the present time as curative, from the results obtained it is the best form of treatment now at our disposal.

The remissions last from months to years. In the case above detailed there was a remission of from six to eight months during which the patient was entirely free from symptoms of the disease. In other instances remissions have lasted from two to three years, although there is always a tendency for the disease to relapse, and each recurrence responds less promptly and less completely to radium

treatment. During the remissions patients may feel entirely well and assume the usual duties connected with their work and social affairs. They are, however, very susceptible to intercurrent infections. A case of fatal pneumonia occurred at the height of the improvement in the remission. Rapid recurrence and death by small gradual or massive hemorrhages or from weakness may occur after benzol or *x*-ray treatment and also, as in the case above described, after a remission produced by radium. Indeed, such rapid termination is common in untreated cases.

Conclusions. (1) Surface applications of radium in leukemia produce striking, indeed remarkable, improvement in (*a*) the blood picture which becomes almost normal, (*b*) in the size of the spleen and glands which are reduced almost to normal, (*c*) in the general condition of the patient, who from an emaciated and weak condition may become plump and strong. (2) The duration of remission is variable; it may last from months to years. (3) The results of radium treatment are *not* regarded as *curative*. It is believed to be, however, the safest as well as the most prompt palliative measure in cases of chronic leukemia whether *refractory* or not to benzol or *x*-ray treatment. From the results of radium therapy in leukemia it is believed to be the best form of treatment now at our disposal.

DISCUSSION

Dr. Henry Sewall, Denver, inquired how long the radium had been allowed to remain at each application?

Dr. Alexander McPhedran, Toronto, asked if radium will always act as well? May not abnormal leukocytes be found in Dr. Ordway's case by careful search even during this period of apparent cure?

He cited a case to show that the spontaneous variations in progress or remissions may be very great. In this case the spleen was very large and there were 500,000 leukocytes per cubic millimeter. In two months the spleen becomes so small as to recede above the costal margin and the leukocytes reduced to 4000. But even then, on careful examination, an occasional myelocyte was found. The symptoms recurred after a few weeks, and he died a year later from hemorrhage from spontaneous rupture of an erroneously enlarged spleen.

Dr. Thomas Ordway, Albany, said that all of the cases of chronic leukemia seen by him, even though previously refractory to *x*-rays and benzol, have responded to radium therapy; a larger series of applications is usually required than was necessary in the case reported. In this case no abnormal cells were to be found in the blood after the treatments have been concluded, though the relative lymphocyte count was increased. When remissions under radium therapy have occurred in leukemia, patients are subsequently more refractory to radium treatment.

In reply to Dr. Sewall's question, he said that the radium was applied to each plotted square for four hours.

SOME STUDIES OF A DIURETIC (THEOCIN)[1]

By HENRY A. CHRISTIAN, M.D.
BOSTON

In 1913 and 1914 there were published by myself and my associates[2] several studies of the action of diuretics on animals with acute experimental renal lesions. In general these studies showed that diuretics in acute experimental nephritis were ineffectual or injurious, very often the latter. In 1915 a brief report[3] was made of observations on the effect of diuretic drugs in patients with chronic nephritis. In a recent Harvey Lecture[4] this same subject is touched upon. Here it is pointed out that frequently when the kidney is damaged, diuretics do not cause a diuresis, or if a diuresis occurs there may be evidence of marked renal fatigue subsequent to the diuresis. Skepticism has been expressed as to the efficiency of diuretic drugs in cases of nephritis in which the kidney is seriously damaged. In these several studies theocin was used as well as other diuretics.

During the past winter further study has been made of the action of theocin in patients with acute or chronic nephritis admitted to the medical wards of the Peter Bent Brigham Hospital. The general

[1] Abstract: Full case reports and charts appear in Arch. Int. Med., 1916, xviii.

[2] Christian, Diuretic Drugs in Acute Experimental Nephritis, Jour. Am. Med. Assn., 1913, lxi, 267. Christian and O'Hare, A Study of the Therapeutic Value of a Diuretic (Theobromin Sodium Salicylate) in Acute Experimental Nephritis, Arch. Int. Med., 1913, xi, 517. Walker and Dawson, The Effect of Diuretic Drugs on the Life of Animals with Severe Acute Nephritis, Arch. Int. Med., 1913, xii, 171. Christian, The Effect of Theobromin Sodium Salicylate in Acute Experimental Nephritis as Measured by the Excretion of Phenolsulphonephthalein, Arch. Int. Med., 1914, xiv, 829. Fitz, The Immediate Effect of Repeated Doses of Theobromin Sodium Salicylate and Theocin on Renal Function in Acute Experimental Nephritis, Arch. Int. Med., 1914, xiii, 945.

[3] Christian, Frothingham, O'Hare and Woods, Am. Jour. Med. Sci., 1915, cl, 666.

[4] Christian, Am. Jour. Med. Sci., 1916, cli, 625.

plan of this study was first to investigate the patient by the usual methods of physical examination, next to study their renal function by several methods, and then to place them on a fixed diet for several days preceding and following one or several doses of theocin. During this latter period some patients had the sodium chloride and nitrogen quantitated in the twenty-four-hour amount of urine; in other patients these quantitations were made in two-hour portions of day urine and one portion of night urine. Following the giving of theocin, certain tests of renal function were repeated and contrasted in result with similar tests before the theocin was given. Three types of cases were studied: patients with acute nephritis, patients with chronic nephritis, and patients with chronic cardio-renal disease.

Summary of Cases of Acute Nephritis. In 6 patients with acute nephritis without demonstrable edema at the time of the tests, with three doses of 0.1 gm. of theocin, a good diuresis was produced in 3, a moderate diuresis in 2, and no diuresis in 1. If there occurred a diuresis, there was an increased sodium chloride excretion, though the amount did not increase parallel to the increase in amount of urine. The excretion of nitrogen sometimes increased, sometimes decreased, in the presence of a diuresis; more often it increased, but not as regularly as was the case with sodium chloride, and the increase in nitrogen did not follow so closely the increase in amount of urine as did the sodium chloride.

Forty-eight hours following the diuretic the index of urea excretion (McLean[1]) decreased in 3 patients and increased in 3. Of the 6 patients only 2 had definitely abnormal indices of urea excretion. One had a very low index. This was a patient who we know to have been free from nephritis several months before these observations, as he was under observation in the hospital for another condition. However, this patient instead of improving while under observation progressed into the picture of a subacute to chronic nephritis. The other patient with abnormal index of urea excretion had a high index which became much higher after the diuresis.

[1] Jour. Exp. Med., 1915, xxii, 212 and 366.

Summary of Cases of Chronic Nephritis. In 5 patients with chronic nephritis, all except 1 of whom had some edema at the time of the tests, theocin in varying doses (totals of 0.3 gm., 0.9 gm. and 1 gm.) produced a moderate diuresis in 1, a slight diuresis in 3, and no diuresis in 1. In all there was an increased excretion of sodium chloride, even in the patient who had no diuresis. The amount of nitrogen excreted was increased in 2 patients and decreased in 3. The index of urea excretion was decreased in 3 patients, increased in 1, while in the fifth the determination was not made close enough to the diuretic to be of any significance. In all of these the index of urea excretion was below normal. In the 2 patients in which the two-hour renal test was carried on during the several days of testing this form of test shows a decreased power of concentration during the day on which theocin was given, with an almost complete return on the day following to the condition existing prior to giving the theocin.

Summary of Cases of Chronic Cardiorenal Diseases. In 6 patients with chronic cardiorenal disease theocin in varying doses (totals of 0.3 gm., 0.9 gm., 1 gm. and 1.5 gm.) produced a marked diuresis in 4 and no diuresis in 2. In the patients who had no diuresis there was no edema present at the time of the tests, and during that period there were no signs of cardiac decompensation. In 1 of the 4 patients with marked diuresis no quantitations of nitrogen and sodium chloride were made. In the other 3 there was a markedly increased excretion of sodium chloride, while in 2 the nitrogen excretion was slightly increased, and in 1 it was decreased. In the 2 patients without diuresis sodium chloride excretion was slightly increased in 1, slightly decreased in the other, while nitrogen excretion was unchanged in 1 and slightly decreased in the other. In the 3 patients with marked diuresis in which the index of urea excretion was determined, 1 showed a slight increase, 1 a slight decrease, and 1 a strikingly large decrease. In the 2 patients with no diuresis, 1 showed an increased and 1 a decreased index, 1 patient in this series had a high index of urea excretion and 1 an index moderately though definitely, below normal. In the others the indices were within normal limits. In the three patients in whom the two-hour renal test was carried out on the several days

before and after giving theocin, this test showed very little difference in the charts on days preceding and following the theocin.

Discussion. In this series of patients it is seen that theocin has no constant diuretic action. In patients with little or no demonstrable edema, theocin may produce a moderate degree of diuresis (expressed roughly as good in 2 patients, moderate in 3, and slight in 3) or it may produce no diuresis (4 patients). In none of our cases of pure nephritis was there any very great amount of edema at the time the tests were made. In four cardiorenal cases, however, there was a very considerable degree of edema, and in these a much greater diuresis was produced by theocin. When a diuresis occurred, almost always sodium chloride excretion was increased, but the increase was not parallel to the increase in fluid, though usually the increase in excretion was most marked in those patients in whom occurred the greatest increase in urine output. Sometimes with rather small increases in urine output, sodium chloride excretion was considerably increased. In contrast to sodium chloride, nitrogen excretion was increased less frequently, and usually to a less degree. In half of the cases studied, nitrogen excretion decreased after giving theocin. Even in patients with a marked diuresis, nitrogen excretion might be but little increased or even decreased.

If we consider the question of the therapeutic efficiency of theocin as a diuretic in the light of the above results we would be justified to express skepticism of its value in patients with relatively little demonstrable edema. In the first place an increased urine output is not constant after theocin, though it often occurs. If we give a diuretic to a patient with acute or chronic nephritis having only moderate edema, what might be considered to be the therapeutic effect we are seeking? In such a case the edema in itself is rarely doing much harm. So to remove a large amount of fluid, even were that the result from giving the diuretic, would not in itself be of much therapeutic value. Very likely the patient is toxic, and shows signs of uremia. In such an event we might seek by a diuretic to increase elimination through the kidney. Theocin in these cases of ours caused usually an increased elimination of sodium chloride and water, but we have no evidence that sodium chloride retention

is harmful unless it is a factor in the production of a disturbing edema. There is more evidence that nitrogenous substances of some kind are toxic, but as we have seen nitrogen elimination is much less constantly increased by theocin and quite often is actually decreased. So from this point of view we might question the therapeutic efficiency of theocin in cases of nephritis with moderate amounts of edema. Perhaps we can assume that the reason for using a diuretic in this type of case is to increase renal efficiency, to stimulate the kidney to increased work. Measured by water or sodium chloride output, theocin might be said to accomplish this; measured by nitrogen elimination, function is little improved, often is made worse. Renal efficiency as measured by the index of urea excretion in cases of acute or chronic nephritis we have found in our cases to be more often decreased after using theocin, so that the evidence here is against rather than in favor of an increase in renal efficiency from the use of theocin.

Now if we turn to cases in which there is a large element of cardiac insufficiency we have found that theocin very commonly, especially when used in combination with digitalis, causes an active diuresis especially in patients with marked edema. In them salt output usually is markedly increased. On the other hand, nitrogen excretion often is but little increased, sometimes actually decreased. In these patients edema is a troublesome symptom. To remove it helps the patient. Theocin is effective in producing a large diuresis and so decreases edema, and in this sense is therapeutically efficient. These patients, as a rule, are not toxic, and removal of nitrogenous substances is not what is sought from theocin. Even in cases of this group a marked diuresis from theocin is often followed by a drop in the index of urea excretion, suggesting that following great renal activity comes a period of depressed renal function. If this is true, then an intermittent dosage with theocin with intervening period in which no diuretic is given is probably the best procedure to follow with cases of the cardiorenal group having considerable or marked edema. In a very considerable number of patients with cardiorenal disease we have found theocin to be effective in this sense used in this way, so that our observations here reported on a few patients with cardiorenal edema in which sodium chloride and

nitrogen elimination and the index of urea excretion were studied are in accord so far as the effectiveness of theocin in producing a diuresis is concerned with our observations on a number of patients in whom these detailed studies were not made.

The study here reported is of relatively few cases and of but one diuretic (theocin). This being the case it must be realized that far-reaching conclusions are unjustified. Those that have been drawn should be regarded as merely suggestive. They are, however, quite in accord with the views previously expressed by myself with regard to diuretics, views based on animal experimentation and various methods of clinical observation.

Summary. A fairly complete study of a small group of patients with acute nephritis or chronic nephritis, or cardiorenal disease, indicates that theocin in patients with slight or no edema has little or no therapeutic value, inasmuch as diuresis is not constantly produced, elimination of nitrogenous substances quite often is slightly if at all increased, and renal function is frequently decreased after giving theocin. In cardiorenal cases with marked edema theocin is of therapeutic value because it produces, especially in conjunction with digitalis, an active diuresis with increased sodium chloride elimination which decreases edema, a troublesome feature in these cases. Inasmuch as there is evidence that, following an active diuresis, renal function is depressed, an intermittent usage of theocin seems preferable to a continuous usage in cardiorenal cases with edema.

DISCUSSION

Dr. L. G. Rowntree, Minneapolis. Were there any observations on water alone as a diuretic?

Dr. J. M. Anders, Philadelphia, said the paper was timely because heretofore we have had no reliable criteria for the use of diuretics; the work will afford these for practical application. In his own practice, he had relied on saline diuretics and one of the members of the caffein series. We should not employ diuretics, however, unless the phthalein test shows a functional capacity equal to 30 per cent. In order to aid elimination we

have been used to giving large draughts of water since water assists in the excretion of all dialyzable substances; was this taken into consideration in the studies?

Dr. W. S. Thayer, Baltimore, said that Dr. Christian had undoubtedy contributed an important piece of work. The conclusions are in accord with clinical experience; he had noted the beneficial effect of diuretics in cardiac disease, and had noted also the danger of continuous use of diuretics in severe renal disease.

Dr. Henry A. Christian, Boston, said Dr. Anders had brought up the question of the phthalein test as index of renal excretion in nephritis in relation to diuretics, but the value of this test for this purpose will depend upon whether a low output is due to chronic passive congestion or to renal insufficiency from nephritis. In the latter if phthalein output is low, diuretics are apt to be ineffectual. As to the influence of water, this was not particularly studied; however, all of the patients were on a constant fluid intake. As to the diuretic value of water, it acts like other diuretics in shortening the lives of experimental nephritic animals, but this action is less marked with water.

THE EXCRETION OF CHLORIDES AND WATER AND THE RENAL FUNCTION IN SERUM DISEASE

By FRANCIS M. RACKEMANN, M.D.
WARFIELD T. LONGCOPE, M.D.
AND
JOHN P. PETERS, M.D.
NEW YORK

Since the classical work of von Pirquet and Schick on serum disease, it has been repeatedly observed that with the edema which appears in the course of this illness, albumin and occasionally casts may occur in the urine, and a few observers have noted suppression of urine, with subsequent albuminuria and cylindruria, during severe immediate or accelerated reactions following a second dose of serum. Though these symptoms are said to be transient, no accurate studies have so far been made to determine whether actual changes take place at this time in the functional activity of the kidneys, and since it has been shown by one of us that repeated injections of foreign protein in sensitized animals may lead to damage of the kidney as well as to the other organs, it seemed important to determine whether the edema, which is often general in serum disease, was associated with any transient impairment of the kidney function.

For this purpose 10 cases of serum disease have been studied. Most of the patients were young adults, 5 below the age of twenty-five; of the remainder 1 was twenty-nine, 1 thirty-one, 1 thirty-six, 1 forty-eight, and 1 forty-nine. None of them gave a history which would suggest any previous disease of the cardiovascular system or of the kidneys, and none presented any signs of chronic diseases when they entered the hospital. Nine cases followed the intra-

venous use of antipneumococcus serum, and one the intraspinous injection of antimeningococcus serum.

The methods employed to study the functional activity of the kidneys have been the following: Immediately after the patient received the first therapeutic injection of serum, which in every instance was horse serum, he was given a suitable diet that contained as nearly as possible a constant quantity of sodium chloride. This varied in different instances, but during the period of the disease in which the diet contained fluid or only eggs, bread, and cereals, the patients received from 2 to 3 grams of salt a day; later, when the diet was increased, the amount of sodium chlorides varied from 6 to 10 grams a day. The total fluid intake was fixed at 2500 c.c. or 3000 c.c., according to the needs of the individual. On this constant intake of sodium chloride and fluid the daily output of urine was measured and the chlorides estimated by the Mohr method. In a few instances the chlorides of the plasma have been determined by the Volhard method, as applied by McLean and Van Slyke[1] at various intervals, before, during, and after the serum sickness. In the same way the total blood urea has been estimated by the urease method, and the index of urea excretion studied according to McLean's modification[2] of the Ambard formula. Together with these procedures the excretion of phenosulphonephthalein has been tested at intervals during the course of the disease.

As most of the cases of serum sickness occurred during convalescence from pneumonia, and since it is known that the excretion of chlorides as well as the nitrogeneous metabolism is greatly disturbed in this disease, it was necessary to use the same methods to study as controls several patients convalescing from pneumonia who had not received serum. Five such cases were followed during their convalescence. During the attack of pneumonia, as is well recognized, the excretion of chlorides is greatly diminished. The plasma chlorides fall below normal, and the amount of urine is small. Three or four days after the crisis the plasma chlorides rapidly rise and the excretion of chlorides increases so that the chlorides retained

[1] Jour. Biol. Chem., 1915, xxi, 361.
[2] Jour. Exp. Med., 1915, xxii, 212.

during the disease are eliminated within a few days. During this time they are excreted in excess of the intake and in high concentration. Very rapidly, however, a balance is established and the normal ratio and excretion is reached.[1]

The curves shown in Chart I are characteristic of the 5 cases studied as controls.

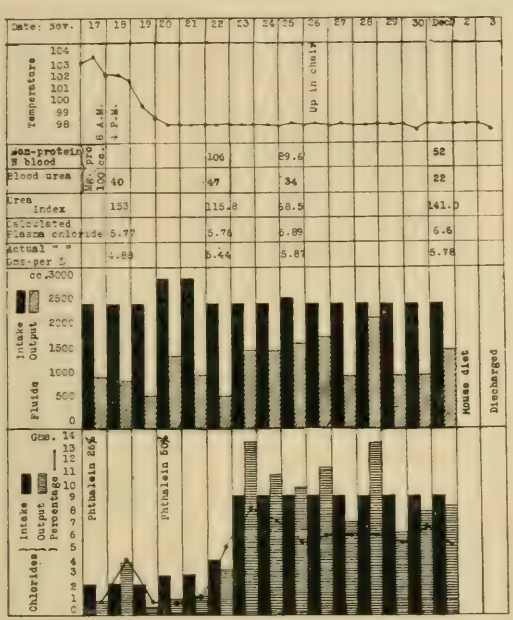

FIG. 1.—M. S., man, aged thirty-four years, with lobar pneumonia, pneumococcus Type 1. The usual course of water and chloride excretion, the changes in non-protein nitrogen, urea and chlorides of the blood and phenolsulphonephthalein excretion during convalescence from uncomplicated lobar pneumonia.

During the convalescence from pneumonia there may be a disturbance in nitrogenous metabolism, the total blood urea varying considerably from the normal figure. For this reason no deduction can be drawn from the estimation of urea and the non-protein nitrogen of the blood in these cases of serum disease. The index of urea excretion, however, remained unaltered in three of the control cases. Table I gives the determination of phthalein for a two-

[1] Peabody, Jour. Exp. Med., 1913, xvii, 71; McLean, Jour. Exp. Med., 1915, xxii, 366.

hour period, of the blood urea, the urea index, and the plasma chlorides in four control cases. In Cases I and IV these estimations were made both before and after the crisis.

TABLE I.—SHOWING PHTHALEIN EXCRETION, BLOOD UREA AND INDEX OF UREA EXCRETION AND PLASMA CHLORIDES IN CASES OF UNCOMPLICATED LOBAR PNEUMONIA

Control cases uncomplicated pneumonia.	Date.	Phthalein.	Blood urea per 100 c.c.	Urea index.	Plasma chlorides, grams per liter.	
I	Oct. 18	26	40	153.0	4.88	before crisis.
	Oct. 20	50	47			
	Oct. 22	..	47	115.8	5.44	after "
	Oct. 25	..	34	68.5	5.87	
	Dec. 1	..	22	141.0	5.78	
II	Jan. 14	64	16	171.0	5.5	after "
III	Jan. 4	46	..	..	..	at "
IV	Nov. 7	56	..	..	..	before "
	Nov. 30	51	..	..	..	after "
	Dec. 1	..	32	113.0	5.52	after "

As compared to these controls a study of the 10 cases of serum sickness showed that during this illness the excretion of phthalein and urea was little affected. Table II gives the estimation of phthalein for a two-hour period, the blood urea, and index of urea excretion in the 10 cases. In Case III the excretion of phthalein has slightly diminished, in Case IV at the onset of serum sickness the phthalein excretion was far below normal and the blood urea distinctly elevated.

Unfortunately the index of excretion was not determined, but before recovery from serum disease the blood urea had fallen to the normal level. In Case IX the blood urea was also high but the index normal. In Case X there was a transient but marked reduction in excretion of phthalein during the serum sickness.

Much more profound changes were, however, observed in the excretion of water and chlorides than in the excretion of nitrogen and phthalein. This was observed in 8 of the 10 cases. The 2 cases that did not show any deviation from the controls were Cases I and II.

Case I received two doses of 90 c.c. of antipneumococcus serum intravenously, which were followed in eight days by mild urticaria lasting forty-eight hours, while in Case II the administration of the same amount of serum intravenously was followed in eight days by a fairly severe urticaria of four days' duration.

The remaining 8 cases fall into two distinct groups. In the first, which comprises 6 cases (Cases III, IV, V, VI, VIII and IX), the following changes were observed. At the onset of serum sickness the excretion of chlorides fell to a low figure, so that on an intake of 5 grams of sodium chloride, less than 1 gram would be eliminated.

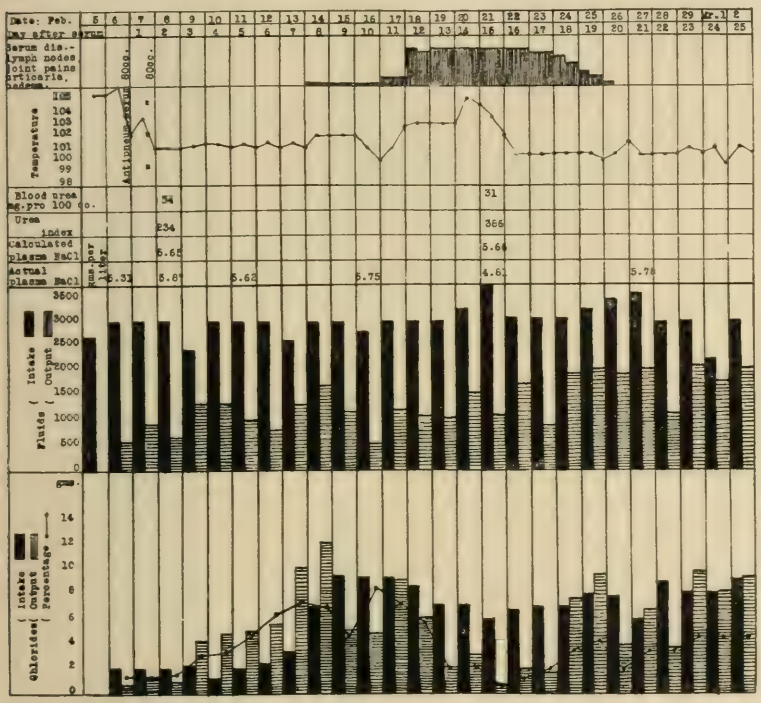

FIG. 2 (Case 5).—W. B., man, aged thirty-one years, with lobar pneumonia, pneumococcus Type 1, with serum disease following the intravenous injection of serum. The course of water and chloride excretion, the changes in blood urea, urea index, plasma chlorides, and excretion of phenolsulphonephthalein during convalescence from pneumonia complicated by serum disease. The severity of the serum disease is indicated by the height of the block in that section.

At the same time the total volume of urine diminished, so that the chlorides were excreted in very low concentration. During this time the addition of 10 extra grams of sodium chloride to the diet in Cases IV and VIII caused no increase in excretion of chlorides in the urine. With recovery from the symptoms of serum sickness the chlorides are eliminated in great excess of the intake, in moder-

ately high concentration, and are often associated with a mild diuresis. One patient, Case VIII, who on an average intake of

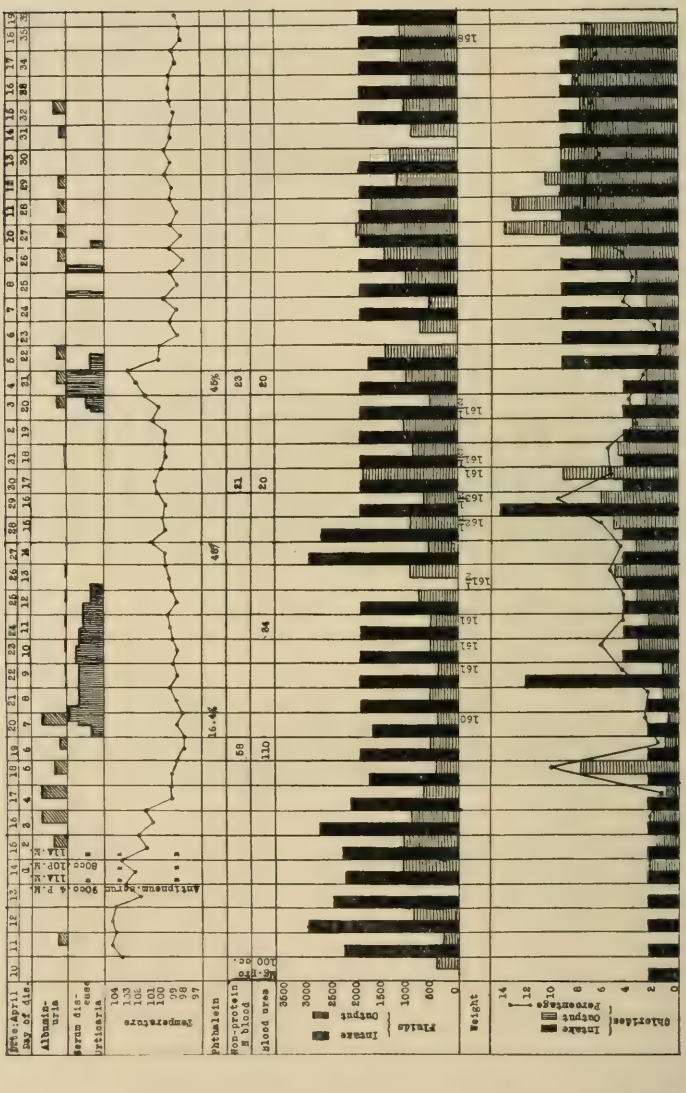

FIG. 3 (Case 4).—M. H., woman, aged forty-nine years, with lobar pneumonia, pneumococcus Type 1, with serum disease following the intravenous injection of serum. The course of water and chloride excretion, the changes in the non-protein nitrogen of the blood, blood urea, and excretion of phenolsulphonephthalein, in convalescence from pneumonia complicated by severe and relapsing serum disease. The severity of the serum sickness is represented by the height of the blocks in that section.

4.5 grams of sodium chloride, had been retaining chlorides during a prolonged attack of serum disease lasting twenty-two days,

eliminated after recovery 12 to 16 grams of chlorides on a daily intake of 6 grams of sodium chloride, while the daily output of urine on an intake of 2500 c.c. of fluid, suddenly increased about 1000 c.c.

The degree of water and chloride retention seems to depend upon the intensity of the serum disease rather than upon the amount of serum given, for the disturbances were quite as marked in one boy of fifteen who received two doses of 40 c.c. of antipneumococcus serum intraspinally as in a man of thirty-one who received a total of 160 c.c. of serum intravenously.

The following charts from Cases IV and V illustrate well the type of alteration observed. In Case V, a man of thirty-one, the critical close of his pneumonia is followed by the usual excessive excretion of chlorides in high concentration. With the onset of serum disease the daily elimination of chlorides immediately falls to 1 to 3 grams a day on the intake of 6 or 7 grams, and the percentage is reduced below 0.2. With recovery from serum disease the retained chlorides are again excreted and the quantity of urine increases.

In Case IV the injection of 240 c.c. of serum in four doses resulted in a severe and relapsing type of serum disease lasting twenty days. It will be seen from the chart that the addition of an extra 10 grams of salt to the diet on the third day of the serum disease was not excreted, and that the same procedure during the intermission between the two severe attacks of serum disease was followed by a very slight response, as evidenced by the moderate increase in the excretion of chlorides during the next forty-eight hours.

The question immediately arises as to whether the chlorides in these cases are retained in the tissues or in the blood. McLean has reported a case of serum disease after pneumonia in which the retention of chlorides was associated with a high plasma chloride. A study of the plasma chlorides in this group seemed to indicate that the chlorides are retained in the tissues rather than in the blood. In one case (V) the plasma chlorides were carefully followed before, during, and after the serum sickness. The results are shown in Table II and in Chart II. Immediately before the crisis the plasma chlorides were somewhat lower than is generally conceded to be the normal figure for the threshold of excretion, which is put at 5.62 grams per liter. At this time there were 5.31 grams per liter.

Immediately after the crisis they rose to 5.87 grams per liter; three days later they were 5.62 grams per liter. The day before serum disease appeared they were 5.75 grams. On February 21, the fourth day of the serum disease, they had fallen to the extremely low figure of 4.81 grams, while on February 27, two days after recovery from serum sickness, they had risen to 5.78 grams, and chlorides were being excreted in large quantities in the urine.

TABLE II.—SHOWING PHTHALEIN EXCRETION, BLOOD UREA AND INDEX OF UREA EXCRETION AND PLASMA CHLORIDES, BEFORE, DURING AND FOLLOWING SERUM DISEASE

Case No.	Before serum disease.				During serum disease.				After serum disease.			
	Phthalein, per cent.	Blood urea, mg.	Urea index.	Plasma chlorides.	Phthalein, per cent.	Blood urea, mg.	Urea index	Plasma chlorides.	Phthalein, per cent.	Blood urea, mg.	Urea index.	Plasma chlorides.
I	48	32	480	..	58	24	254	..	..	22	436	
						24	410	..	..	18	466	
II	30	45	..	..	54	31	..	..	..	26		
	59	36	..	..	..	32						
III	..	..	..	..	45	32	..	..	60	28		
					33							
					47							
IV	..	..	..	..	16.4							
					48	34						
						20						
					45	20						
V	75	34	234	5.31	64	31	386	4.81	..	..	..	5.78
				5.87								
				5.62								
				5.75								
VI	..	..	..	..	80	24						
						31						
VII	54	16	300	6.125	58	11	148	6.50	62	10	235	6.56
VIII	..	39	..	..	50	33						
					62	29						
						16						
IX	55	..	..	..	68	46	126	..	64	12	163	
						65	151	..	74	24	133.75	
X	50	40	111	..	18	20	113	..	65			

We may therefore conclude that in this group of cases the marked retention of water and chlorides takes place in the tissues and is associated regularly with albuminuria of mild degree with the presence of casts in the urine and occasionally (Cases III and IV) with a transient disturbance in the excretion of phthalein.

In the second group, which comprises only 2 cases (VII and X), the excretion of salt and water is affected in a different manner. Both of these cases are women, Case VII, aged forty-eight years, and Case X, twenty-nine years. Case VII received three intravenous

injections of 80 c.c. of serum, which was followed on the seventh day by mild serum disease consisting of urticaria and enlargement of lymph nodes, but which persisted for ten days. There was no excessive retention of chlorides or water, but the patient was incapable of concentrating the chlorides in the urine and excreted fair quantities of chlorides in low concentration. This is well illustrated in Chart IV. It will be seen that on two occasions, March 31 and April 5, when chlorides were excreted in excess of the intake, an actual diuresis occurred.

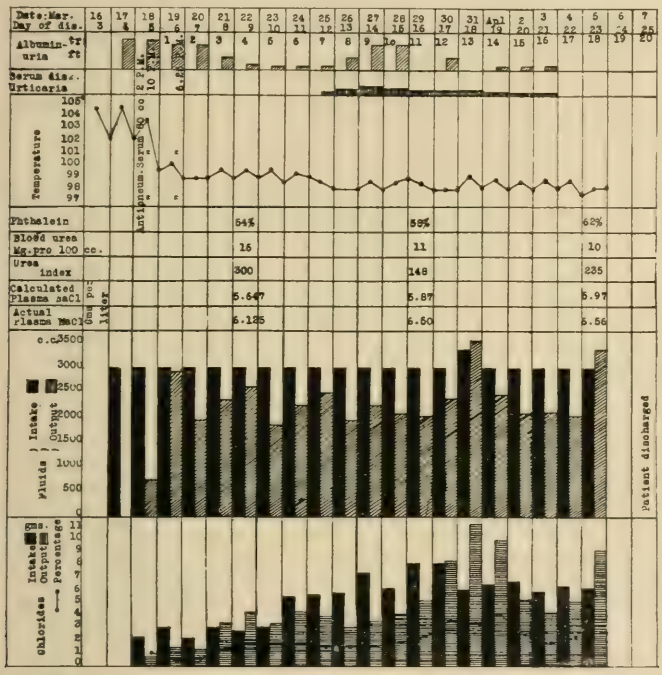

FIG. 4.—E. F., woman, aged forty-eight years, with pneumonia, pneumococcus Type 1, with serum disease following the intravenous injection of serum. The course of water and chloride excretion, the changes in blood urea, the urea index, the plasma chlorides and phenolsulphonephthalein excretion during convalescence from pneumonia complicated by serum disease. The severity of the serum disease is represented by the height of the blocks in that section.

In Case X the same type of excretion was observed. In both instances there were albuminuria and cylindruria, which disappeared after the subsidence of the serum disease. In this group, therefore,

the serum disease was accompanied by a hyposthenuria. A study of the blood chlorides in Case VII showed that they were always high, before, during, and after the attack of serum disease, but tended to rise during the serum disease from 6.25 grams per liter to 6.5 grams per liter. In this group, therefore, it is evident that there is a retention of chlorides in the blood, though it is impossible to exclude the tissues as well. They are, however, excreted through the kidneys only in dilute solution, which results in what Schleyer has termed hyposthenuria. It is possible that in these two instances there was some previous injury to the kidney which resulted in this type of excretion. But so far as could be determined from subsequent study of one of these patients, these alterations were not persistent.

Discussion. These studies show very definitely that during serum disease there is often a marked but transient retention of chlorides and of water associated frequently with slight albuminuria and cylindruria and occasionally with impairment of the excretion of phenolsulphonephthalein. In 5 of the 10 cases there was obvious edema, with gain in weight. In the other cases there was no edema and no gain in weight. In the first group it is probable that the plasma chlorides are below normal, that some disturbance occurs primarily in the tissues during the intoxication which causes a retention of salt and water in this situation. This may give rise to a generalized edema. There may, too, be some functional impairment in the excretory action of the kidneys. In the second group, in which the plasma chlorides are high, the disturbance consists principally in the impaired elimination of chlorides and the inability to concentrate these organic salts in the urine. In the 2 cases in this group edema was not observed.

THE OCCURRENCE OF LIVING TUBERCLE BACILLI IN RIVER WATER CONTAMINATED BY SEWAGE FROM A HEALTH RESORT

By LAWRASON BROWN, S. A. PETROFF
AND
F. H. HEISE
SARANAC LAKE, N. Y.

There are many missing links in the etiological chain in tuberculosis, and this paper is the outcome of an attempt to supply from time to time some of these missing links. Several years ago a number of observers claimed that tubercle bacilli occurred in the feces of a large number of patients with pulmonary tuberculosis. We attempted to verify this, and Laird and Kite, in the laboratory of the Trudeau Sanatorium, found that the feces contained viable tubercle bacilli in 90 per cent. of all patients with open lesions. We now question if this figure is not too low, for one of us (Petroff) found them in all of thirty-two cases examined and was able to cultivate them, which, as far as we know, no one had done before, in 59 per cent. The ease with which guinea-pigs could be infected with tubercle bacilli in the feces suggested that a study should be made of water of streams contaminated with sewage. The sewerage system of Saranac Lake at present empties into the Saranac River just below the village. (Only four or five small houses in the whole village are not connected with this system.) We studied the surface and deeper waters, and in some instances the mud above and at the outlet of the sewer and at different distances down stream (200 yards, 400 yards, 2.9 miles—measured along a road which does not closely parallel the river—3.5 and 12 miles). (These distances were determined by the occurrence of bridges across the river.)

The flow of the stream was estimated to be about two to four miles per hour.

The Technic. Large bottles were used to collect the water at the outlet of the sewer. To obtain the water at different levels the covering of the mouth of the bottle was left in place until the bottle was immersed to that level.

Farther down the river a different method was used for studying the surface contamination. Strips or bags of sterile cheese-cloth were attached to wires and stretched across the surface of the stream and allowed to remain in position from one to two hours, when they were put into sterile-covered pails and carried to the laboratory.

The cloth was very carefully washed in sterile water. The wash water was then put into wide-mouthed bottles, saturated with NaCl, and let stand in the dark for several hours. At the end of that time the scum was collected with sterile spoons and transferred to 50 c.c. centrifugal tubes. Ten c.c. of normal NaOH was added to each tube, which was incubated at 37° for one-half hour. The contents of the tubes were then neutralized with normal HCl, centrifugalized, and part of this sediment was studied microscopically, part inoculated into egg media, and part injected into guinea-pigs.

The Cultures. All the cultures were contaminated, due very likely to the presence of many moulds and spore-forming organisms in the river water. At this time the gentian-violet media (Petroff) was not in use.

The Microscopic Study. Every smear preparation but two, taken from below the surface, from the outlet of the sewer to a point 3.5 miles down stream, showed the presence of acid-fast organisms. (No acid-fast organisms were found above the outlet or 12 miles below the outlet.)

The Inoculation of Guinea-pigs. Our work upon the feces does not incline us to believe that acid-fast organisms other than tubercle bacilli occur frequently in the feces of tuberculous patients, for under certain conditions we have been able to infect guinea-pigs in nearly every instance in which we found acid-fast organisms in the feces of tuberculous patients. It will be noted from the table

that acid-fast organisms occurred in most of the specimens, less often deep in the water than upon the surface as far at least as 3.5 miles from the mouth of the sewer. Unfortunately the next point

Distance from sewer mouth.	Location of sample.			Date and time.	Acid-fast organism.	Guinea-pigs.	Cultures contaminated.
	Surface.	Deep.	Mud.				
Mouth . .	. .	+	. .	June 25, 1914 9.30 A.M. Sunny	++	A. Tub. B. Tub.	+
Mouth . .	+	. .	. .	June 25, 1915 9.30 A.M Sunny	++	A. Died. B. Tub.	+
Down stream 200 yards	+	. .	. .	June 25, 1914 10 A.M. Sunny	+	A. Tub. B. Tub.	+
400 yards .	+	. .	. .	June 25, 1914 10 A.M. Sunny	+	A. Tub. B. Tub.	+
400 yards .	. .	+	. .	June 25, 1914 10.30 A.M. Sunny	+	A. Tub. B. Non-tub.	+
2.9 miles .	+	. .	. .	Aug. 1, 1914 10 A.M. Cloudy	+ Pus cells	A. Lost. B. Tub.	+
2.9 miles .	. .	+	. .	Aug. 1, 1914 10 A.M. Cloudy	0	A. Non-tub. B. Non-tub.	+
3.5 miles .	+	. .	. .	Aug. 1, 1914 10.30 A.M. Cloudy	+	A. Non-tub. B. Non-tub.	+
3.5 miles .	. .	+	. .	Aug. 1, 1914 10.30 A.M. Cloudy	0	A. Non-tub. B. Non-tub.	+
2.9 miles .	+	. .	. .	Sept. 25, 1914 9.30 A.M. Cloudy	+	A. Tub. B. Tub.	+
3.5 miles .	+	. .	. .	Sept. 25, 1914 10.30 A.M. Cloudy	+	A. Non-tub. B. Non-tub.	+
2 9 miles .	+	. .	. .	July 6, 1915 9.30 A.M. Sunny	+	A. Non-tub. B. Non-tub.	+
2.9 miles .	. .	. .	+	July 6, 1915 9.30 A.M. Sunny	+	A. Non-tub. B. Non-tub.	+
3.5 miles .	+	. .	. .	July 6, 1915 10 A.M. Sunny	+	A. Non-tub. B. Non-tub.	+
3.5 miles .	. .	. .	+	July 6, 1915 10.30 A.M. Sunny	+	A. Non-tub. B. Non-tub.	+
12 miles .	+	. .	. .	April 12, 1916 45 min.	0	A. Non-tub. B. Non-tub.	Cultures negative.
Above outlet	+	. .	. .	April 13, 1916 1 hour	0	A. Non-tub. B. Non-tub.	

at which we judged we could study the water was at least twelve miles below the sewer's outlet. Here no acid-fast organisms were found, but colon bacilli occurred in small numbers. We believe these acid-fast organisms are tubercle bacilli, for from the sewer's mouth to a distance of at least three miles down stream these acid-fast organisms were capable of producing tuberculosis in guinea-pigs when the sun was not shining. On sunny days the acid-fast organisms when obtained 2.9 miles down stream produced no tuberculosis. When we could discover no particles of feces in the water we found no viable tubercle bacilli.

The water above the outlet contained no acid-fast organisms on smear.

It should be noted that Jessen and Rabinowitch at Davos found tubercle bacilli only 100 meters below the outlet of the sewer.[1]

SAMPLE 1. From deep water at mouth of sewer. June 25, 1914. 9.30 A.M. Sunny.

Slides. Positive; numerous acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. September 15, 1914, killed.

Inguinal glands very much enlarged; abscess at seat of inoculation. Many tubercles in the liver and spleen, few in the lungs; bronchial glands very much enlarged. Smear's from spleen and liver positive to acid-fast organisms.

SAMPLE 2. From surface water at mouth of sewer. June 25, 1914. 9.30 A.M. Sunny.

Slides. Positive for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. A died July 31.

Organs congested; bronchial glands enlarged; smear of suspected parts negative to tubercle bacilli.

Autopsy. B killed September 15, 1914.

Spleen very much enlarged and granular; inguinal glands very much enlarged; liver enlarged, containing many tubercles. Bron-

[1] Ztschr. f. Tub., 1910, xvi, 275.

chial glands very much enlarged. Smears from the suspected parts showed many acid-fast organisms.

SAMPLE 3. From surface 200 yards down stream. June 25, 1914. 10 A.M. Sunny.

Slides. Positive for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. A killed September 15, 1914.

Right inguinal gland size of a large pea, containing thick pus (slide and tubes made). Spleen enlarged and nodular, full of small tubercles. Slide shows gland positive and spleen negative for acid-fast organisms.

Autopsy. B killed September 15, 1914.

Right inguinal gland size of a large pea, containing thick pus (slide and tubes made). Spleen enlarged and nodular, full of small tubercles. Slide showed gland positive and spleen negative, for acid-fast organisms.

SAMPLE 4. From surface 400 yards down stream. June 25, 1914. 9.30 A.M. Sunny.

Slides. Positive for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. A killed September 15, 1914.

Superior inguinal glands enlarged; spleen enlarged and nodular; few tubercles. Slide showed gland positive for acid-fast organisms.

Autopsy. B.

Superior inguinal glands enlarged; spleen enlarged and nodular. Slide showed gland and spleen positive for acid-fast organisms.

SAMPLE 5. From deep water 400 yards down stream. June 25, 1914. 10.30 A.M. Sunny.

Slides. Positive for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. Killed September 15, 1914.

A. Inguinal glands slightly enlarged; spleen slightly enlarged but not nodular; lung apparently normal; liver normal. Smears showed only few acid-fast organisms.

B. Inguinal glands slightly enlarged; lung and liver normal; no acid-fast organisms on the smears.

SAMPLE 6. From surface 2.9 miles down stream. August 1, 1914. 10 A.M. Cloudy.

Slides. Positive for acid-fast organisms; some pus cells.

Cultures. Contaminated.

Guinea-pigs. A and B. A was lost.

Autopsy. B killed September 22, 1914.

Inguinal glands very much enlarged; spleen enlarged and nodular; few tubercles in liver; lungs apparently normal; bronchial glands very much enlarged; spleen, liver, and glands showed numerous acid-fast organisms.

SAMPLE 7. From deep water 2.9 miles down stream. August 1, 1914. 10 A.M. Cloudy.

Slides. Negative for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. Killed September 22, 1914.

Apparently normal, with the exception of the bronchial glands which, were slightly enlarged. Smear preparation showed no acid-fast organisms.

SAMPLE 8. From surface 3.5 miles down stream. August 1, 1914. 10.30 A.M. Cloudy.

Slides. Positive for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. September 22, 1914.

A. Inguinal glands appeared to be slightly enlarged; spleen, liver and lung normal; glands were mashed but no acid-fast organisms found.

B. Apparently normal. No acid-fast organisms found.

SAMPLE 9. From deep water 3.5 miles down stream. August 1, 1914. 10.30 A.M. Cloudy.

Slides. No acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and C.

Autopsy. September 22, 1914.

A. Apparently normal.

C. Apparently normal.

SAMPLE 10. From surface water 2.9 miles down stream. September 25, 1914. 10 A.M. Cloudy.

Slides. Positive for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. Killed November 2, 1914.

A. Superficial inguinal glands slightly enlarged; spleen very much enlarged and nodular; few tubercles in lung and liver; smears positive for acid-fast organisms.

B. Superficial inguinal glands slightly enlarged; spleen slightly enlarged but not nodular; lungs apparently normal. Smears showed few acid-fast organisms.

SAMPLE 11. From surface 3.5 miles down stream. September 25, 1914. 10.30 A.M. Cloudy.

Slides. Positive for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. Killed November 2, 1914.

A. Abscess at seat of injection. No tuberculosis.

B. No tuberculosis.

SAMPLE 12. From surface 2.9 miles down stream. July 6, 1915. 9.30 A.M. Sunny.

Slides. Positive for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. Killed October 2, 1915.

A. Apparently normal.

B. Apparently normal.

SAMPLE 13. From mud 2.9 miles down stream. July 6, 1915. 9.30 A.M. Sunny.

Slides. Positive for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. Killed October 2, 1915.

A. Apparently normal.

B. Apparently normal.

SAMPLE 14. From surface 3.5 miles down stream. July 6, 1915. 10 A.M. Sunny.

Slides. Positive for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. Killed October 2, 1915.

A. Apparently normal.

B. Apparently normal.

SAMPLE 15. From mud 3.5 miles down stream. July 6, 1915. 10 A.M. Sunny.

Slides. Positive for acid-fast organisms.

Cultures. Contaminated.

Guinea-pigs. A and B.

Autopsy. Killed October 2, 1915.

A. Apparently normal.

B. Apparently normal.

SAMPLE 16. From surface 12 miles down stream. Collected forty-five minutes. April 12, 1916.

Slides. Negative for acid-fast organisms.

Cultures. Negative.

Guinea-pigs. A and B.

Autopsy. June 7, 1916. Lungs, liver, spleen and glands apparently normal. (A and B.)

SAMPLE 17. Above outlet of sewer. Collected one hour. Surface. April 13, 1916.

Slides. Negative for acid-fast organisms.

Cultures. Negative.

Guinea-pigs. A and B.

Autopsy. June 7, 1916. Lungs, liver, spleen and glands apparently normal. (A and B.)

A REPORT ON THE TREATMENT OF PERNICIOUS ANEMIA BY TRANSFUSION AND SPLENECTOMY

By H. Z. GIFFIN, M.D.
ROCHESTER, MINN.

It is difficult to appreciate the fact that pernicious anemia is at present an incurable and fatal disease which in some respects is more to be dreaded than cancer. Its relapses, remissions, and merciless progressive course impress upon us the necessity for a universal study of its manifestations. A thorough trial of splenectomy in the treatment of pernicious anemia is therefore warranted, though a consideration of the results is at present necessarily confused by fallacies and insufficient data. There is so far no evidence that splenectomy has cured pernicious anemia, but there are definite indications of consistent temporary improvement in a majority of instances.

Our early experience with splenectomy for pernicious anemia was discouraging. During the past two years, however, it has become evident that a marked reaction and a consistent temporary gain, at least for a period of months, follows splenectomy in selected cases, and surgical treatment has been more frequently suggested after a frank explanation to the patients concerning the course of the disease, the inadequacy of present methods of treatment and the experimental nature of the procedure.

In February, 1910, the spleen was removed from a patient (A 7040) who suffered from severe attacks of epistaxis and had a very large spleen, an icteroid tinge, and a blood picture of pernicious anemia including the presence of megaloblasts. Splenectomy was advised, not with the specific idea of applying that treatment to pernicious anemia, but largely because of the great size of the spleen

and the somewhat indefinite characteristics of the clinical features of the case. The patient did not report himself as improved, and died three years after operation with pneumonia.

Experience may show that cases of this type, in which there is a very large spleen, a hemolytic type of anemia, and a blood picture of pernicious anemia may better be grouped separately, as suggested by Moffit, but they cannot at present be omitted from consideration in a study of this character.

The remaining patients of this series were operated on between August 1, 1914, and April 1, 1916. The records extended up to June 1, 1916, from 23 months to 3 months following operation; most of them, however, were for periods of less than 1 year.

Pre-operative Transfusion. Pre-operative transfusion has been done in 19 cases, from one to four transfusions having been given in each instance. A marked gain followed transfusion in 8 cases. Very rapid and decided gains were seen in 2 patients. In 1 the hemoglobin rose from 10 to 40 per cent., with a gain of 2,000,000 red cells in one month; in the other the hemoglobin rose from 16 to 59 per cent., with a gain of 1,500,000 red cells in one month. Each of these patients received two transfusions. In 6 there were gains of only a few points and in 4 there was no definite improvement. In 1 the hemoglobin percentage and erythrocyte count fell but later after splenectomy improvement occurred.

In general, pre-operative transfusions have proved valuable in improving the general condition of the patient and in favorably affecting the blood picture. The hemoglobin percentage and the red cell count have been moderately raised and the characteristics of the blood count favorably affected. Our knowledge of the hemopoietic system indicates that a consistently low leukocyte count with relative and absolute reduction in polymorphonuclear cells is to be interpreted as the result of severe injury to the bone-marrow. Transfusion is usually followed by a gradual slight rise in the leukocyte count and an increase in the absolute number of polymorphonuclear cells. This reaction is not, however, to be compared in degree with that following splenectomy which, on the other hand, must be considered in the light of postoperative leukocytosis in general.

Splenectomy. That definite benefit for a period of months follows splenectomy in a high percentage of the cases seems to be clearly indicated by a study of this series. Of 28 patients recovering from operation, there was a gain during the first period of 3 months in 22 (78 per cent.). During the second period of 3 months, 11 (68 per cent.) of 16 patients then living maintained their gain. This gain represents a satisfactory, and in several instances a remarkable, improvement in the blood picture and the general condition. It has, however, little relationship to spinal-cord symptoms or signs. Two living patients have maintained a satisfactory condition for one year, 3 for nine months and 3 for six months.

In the course of pernicious anemia splenectomy seems to cause a more profound immediate reaction than any other form of treatment. This is demonstrated by our observations chiefly in three ways: (1) by an improvement in the blood picture and a change in its characteristics; (2) by a gain in the general condition; and (3) by a fall in the values of the blood-derived pigments in the duodenal contents.

1. The Blood Picture. The very prompt occurrence of leukocytosis with a corresponding increase in the relative and absolute polymorphonuclear neutrophile count, together with showers of normoblasts, is indicative of a very marked reaction after splenectomy. The average leukocyte count in these cases within a few days of operation was 11,531. A very high polymorphonuclear count was almost constant. This leukocytosis persisted at least for a period of months. One month after operation it averaged 11,473. In cases of which we have record from three to six months following splenectomy it averaged 10,283. The leukocytosis following splenectomy for pernicious anemia differs from the leukocytosis following operations in general both in degree and in persistence. The polymorphonuclear cells, it is agreed, have their origin in the bone-marrow, and their increase may be either the result of bone-marrow stimulation or of decreased blood destruction. No similar reaction is seen following transfusion.

Large numbers of normoblasts were found in the blood smears in 25 cases. The average was 56 in a count of 300 leukocytes. This is exclusive of 1 case in which 536 were recorded.

The gain in hemoglobin is gradual in most cases. The average gain in 20 patients, whose condition is satisfactory, was from 38 per cent. just preceding splenectomy to 72 per cent. at periods varying from one month to six months following operation. In 3 patients it reached 90 per cent. or more.

The increase in the erythrocyte count ran parallel to the rise in hemoglobin. The average erythrocyte count in the 22 cases showing a gain was 2,000,000 just preceding splenectomy, and 3,490,000 at periods varying from one month to six months after operation. In 1 patient it reached 5,200,000 cells; in 7 it rose to over 4,000,000. This improvement was independent of pre-operative transfusion as is evidenced by the fact that 9 patients in whom pre-operative transfusion was not given showed an average gain from 1,900,000 to 3,700,000. On the other hand, the greatest average gain was seen in 13 patients as a result of combined pre-operative transfusion and splenectomy—an average gain from 1,200,000 to 3,500,000. Post-operative transfusion has been given only in relapses, and not as a routine procedure following splenectomy.

It seems to be clear, therefore, that the blood picture is more decidedly and consistently influenced by splenectomy than by any other method of treatment. It has not yet been shown that this improvement is more than temporary. A polymorphonuclear increase which persists for months, great numbers of normoblasts, and a gradual rise in the hemoglobin and the red-cell count are most prominent.

2. The General Condition. An improvement in appetite and in general strength has been noted during the early weeks following splenectomy. This has been recorded even before any decided improvement in the blood has taken place. The patients seemed to be less toxic. All but 2 promptly lost their icteroid tinge. Elimination or partial elimination of some product of altered metabolism or hemolysis would explain the change in the general condition. The psychic effect of surgical treatment has been minimized by a previous explanation of our incomplete knowledge concerning the results.

3. The Fall in the Values of the Blood-derived Pigments in the Duodenal Contents. The increase of urobilin in stools of

patients suffering with hemolytic types of anemia and its marked decrease after splenectomy have been demonstrated by Eppinger and his co-workers. The clinical importance of the estimation of urobilin in the excretions in various types of anemia is shown by the work of Wilbur and Addis. The quantitative estimation of urobilin and urobilinogen spectroscopically in Wilbur and Addis units has been successfully applied to the duodenal contents by Schneider. We have estimated the values of the blood-derived pigments in the duodenal contents of 34 patients and our findings in general corroborate those of Schneider. The only results I report at this time were obtained in 9 cases of this series. The very striking fall in the values of the blood-derived pigments after splenectomy would seem to indicate a favorable effect with respect to the hemolytic factor. The values frequently run parallel to the degree of icterus (Table III). In 1 case the total estimation of urobilin and urobilinogen fell from 6000 units before operation to 800, twenty-one days afterward; in another from 5000 units to 200 units. That this marked reduction in bilirubin, urobilin and urobilinogen in the duodenal contents will prove constant or that it will obtain at a later period, after splenectomy, we have yet no indication.

Can we formulate what might be termed a balance between the hemolytic and myelotoxic factors in a given case? Between blood destruction and blood production? The values for the blood-derived pigments, it would seem, should in some measure be an index of hemolysis; on the other hand, the characteristics of the blood picture, if we can properly interpret them, are doubtless expressive of the condition of the bone-marrow. Decided fluctuations in the leukocyte count and in the characteristics of the differential count are seen in many cases of this series, both before and after transfusion, and before and after splenectomy. There is considerable evidence to indicate, however, that a consistently low leukocyte count with a reduction of the polymorphonuclear neutrophiles is indicative of severe bone-marrow insufficiency. Certainly a constant complete inversion of polymorphonuclear and lymphocyte percentages, that is, a very low polymorphonuclear percentage with a high lymphocyte percentage, is an unfavorable indication, though it does not mean that a subsequent remission may not occur. If in

spite of active hemolysis a patient with high hemolytic values is able to maintain a blood picture with favorable characteristics and only moderate anemia, there should be present an active bone-marrow and the case would appear to be a more favorable one for splenectomy. Irrespective of high or low hemolytic values, if the leukocyte count is consistently low with an inversion of the differential count and the anemia extreme and showing no reaction after transfusion or medicinal treatment, the case would seem to be an unfavorable one because of probable advanced pathology in the bone-marrow.

Age. The largest number of patients (12) were between 40 and 50 years of age. One was in the second decade, 3 were in the third, 5 in the fourth, 8 in the sixth, and 2 in the seventh.

The progress of the patient in its relationship to age cannot at present be ascertained from a study of these cases. In general the older patients presented less evidence of active hemolysis and more evidence of marrow damage. The patients of middle age were of both the hemolytic and myelotoxic types, while in younger patients hemolysis was usually active. The severity of the disease varied with the individual case irrespective of age, save that the oldest patients were prone to a chronic form with less definite remissions. While the younger patients probably are capable of more benefit as a result of bone-marrow stimulation and an amelioration of the hemolytic factor, many patients of the fourth and fifth decades have shown remarkable gains.

Weight of Spleen. The average weight of the spleens removed in this series was 422 grams, exclusive of two very large spleens weighing respectively 1120 grams and 1600 grams. In only 2 cases did the spleen weigh less than 175 grams. The very small spleen is usually present in the late stages of pernicious anemia and a moderately enlarged spleen is generally found when hemolytic activity is marked. Splenectomy influences chiefly the hemolytic factor of the disease and one might argue that the presence of a moderately enlarged spleen is a point of evidence in favor of splenectomy.

Operative Mortality. In this group of 31 cases there were 3 operative deaths, giving an operative mortality of 9.7 per cent.[1]

[1] Forty-seven splenectomies for pernicious anemia have been done to September 1, 1916, with 3 operative deaths, an operative mortality of 6.4 per cent. There have been no deaths in the last 29 cases.

There is no apparent reason why the operative mortality of splenectomy for pernicious anemia should not be low when a proper operative selection has been made. The spleen is relatively small, adhesions usually insignificant and the technical procedures not difficult. The risk of surgical treatment is decidedly increased in patients with severe anemia and every endeavor should be made to improve the hemoglobin to 35 per cent. or 40 per cent. and the erythrocyte count to 1,500,000 cells.

A consideration of the features presented by the three patients who died following operation reveals that one of them was distinctly not a case for surgical treatment. The hemoglobin was 19 per cent., even after two transfusions, and a consistently low leukocyte count was present. The other 2 operative deaths were similar in character and presented unusually striking features. The patients died respectively on the third and fourth days after having suddenly developed fever as high as 106° and delirium, in 1 case associated with hyperpnea and pulmonary edema and in the other persistent vomiting with ultimate coma. Postmortem examination in both instances failed to show a sufficient cause for death. These fatal attacks may have been the result of operation at a time of recrudescence or impending crisis; in one instance acidosis is a probability. Neither of these patients was in a weakened condition before operation, but both of them for two weeks previous to operation showed a falling hemoglobin, a decrease in the red blood cell count, and a low and falling leukocyte count, all of which would at present be regarded as points in evidence against a recommendation for surgery.

Postoperative Death. Five patients who recovered from operation died subsequently. In 2 the downward course was not averted by splenectomy and death occurred at home within three months. In 1 of these patients there was a slight gain in the condition of the blood but a double femoral thrombophlebitis developed and she died with septic manifestations. In the second patient there was no reaction either in the general condition or the blood and a steady decline occurred. The spleen in this instance was very much above the average size for pernicious anemia, weighing 1120 grams. A third patient died at nine months after decided improve-

ment which was maintained for approximately six months. A fourth patient died at twelve months after gaining to 90 per cent. hemoglobin and 4,000,000 red cells and maintaining a good condition for seven months. The fifth patient died three years after splenectomy; his postoperative course was never determined.

Relapses. Three living patients have had relapses, 2 within six months following operation after an improvement during the first period of three months, and 1 at fourteen months after recovery from a previous relapse at nine months. Two of these who were treated by transfusions at the time of relapse have again had remissions. Three additional patients have never shown evidence of definite gain since splenectomy.

Summary. 1. There is no evidence that splenectomy has cured pernicious anemia.

2. A review of 31 cases of splenectomy for pernicious anemia demonstrates a definite gain in the blood, the weight, and the general condition during the first three months of the postoperative period in 78 per cent. of the cases; during the second three months' period, 68 per cent. of living patients maintained their gain.

3. A consideration of the advisability of splenectomy would seem to be warranted at present chiefly in young and middle-aged patients of good general resistance, who show evidence of active hemolysis and in whom the spleen is moderately enlarged.

4. The estimation of the blood-derived pigments in the duodenal contents is valuable in determining the degree of hemolytic activity present at a given time. A comparison of the degree of hemolysis with the severity of the anemia would seem to be indicative of the productive power of the bone-marrow.

5. Pre-operative treatment, especially transfusions, should be employed to influence the general condition of the patient and to improve the characteristics of the blood picture. The operative risk is increased when the hemoglobin is below 35 per cent. and the erythrocyte count less than 1,500,000 cells.

6. Postoperative transfusions have not been given as a routine procedure but transfusions have been successfully employed in postoperative relapse.

TABLE I.—SPLENECTOMY FOR PERNICIOUS ANEMIA

Total (April 1, 1916)	31 cases
Operative deaths	3 (9.7 per cent.)
Recovered from operation	28
Marked and continuous gain after splenectomy during the first three-month period	22
Number of cases recorded during second three-month period	16
Number of patients maintaining gain during second three-month period	11
Relapse	3
Postoperative death	5

TABLE II.—SPLENECTOMY FOR PERNICIOUS ANEMIA. CONDITION OF PATIENTS IN THREE-MONTH PERIODS AFTER OPERATION WITH RESPECT TO BLOOD AND GENERAL CONDITION[1]

	Case.		Date of operation.	Operative death.	Months.				
					3	6	9	12	15
1	7040	E. P. F.	Feb. 10, 1910	..	−	?	..	..	D'
2	112160	D. M.	Aug. 11, 1914	..	+	+	−D		
3	98744	M. S.	Dec. 2, 1914	..	−D				
4	122468	J. B. M.	Jan. 23, 1915	..	−D				
5	124257	M. S.	Mar. 10, 1915	..	+	+	−R	+	−R
6	127677	C. H.	April 17, 1915	D					
7	129678	O. D. B.	June 4, 1915	..	+	+	+	+	
8	128367	J. H. D.	June 5, 1915	..	+	+	+	+	
9	131876	E. S.	June 24, 1915	..	+	+	−R	D	
10	131901	R. C.	July 3, 1915	D					
11	136882	M. J. F.	Aug. 2, 1915	..	+	+	+		
12	134484	W. G.	Aug. 31, 1915	..	+	−R	+		
13	139695	F. L.	Sept. 8, 1915	..	+	−R	+		
14	140045	G. L.	Sept. 30, 1915	..	+	+	+		
15	142349	E. O.	Oct. 1, 1915	..	+	+	+		
16	141771	H. F.	Oct. 12, 1915	..	+	+			
17	142587	H. W. L.	Oct. 15, 1915	..	−	−			
18	140970	W. A. S.	Oct. 19, 1915	..	+	+			
19	133078	C. A.	Oct. 25, 1915	D					
20	134232	J. N.	Oct. 26, 1915	..	−	−			
21	147503	E. F.	Dec. 31, 1915	..	+	+			
22	150807	W. E. B.	Feb. 2, 1916	..	+				
23	151088	M. R.	Feb. 14, 1916	..	+				
24	150229	E. S.	Feb. 23, 1916	..	+				
25	151665	F. W. N.	Feb. 24, 1916	..	+				
26	152922	W. H.	Mar. 10, 1916	..	+				
27	152671	H. L.	Mar. 15, 1916	..	+				
28	136512	C. G. T.	Mar. 17, 1916	..	−				
29	154493	D. D. H.	Mar. 25, 1916	..	+				
30	153395	L. C. H.	Mar. 29, 1916	..	+				
31	151646	B. N.	Mar. 29, 1916	..	+				

[1] In this table + = gain; − = loss; R = relapse; D = death.
[2] Death at end of three years.

TABLE III.—ESTIMATION OF HEMOGLOBIN-DERIVED PIGMENTS IN DUODENAL CONTENTS. WILBUR AND ADDIS UNITS (SCHNEIDER TEST)

Case.	Number.	Time before and after splenectomy.	Color.	Bilirubin.	Urobilin.	Urobilinogen.	Total.
5	124257 M. S.	12 months after	...	+	400	0	400
22	150807 W. E. B.	37 days after	Yellow	++	700	0	700
24	150229 E. S.	30 days after	Yellow	+	1700	0	1700
25	151665 F. W. N.	34 days after	Yellow	...	600	0	600
26	152922 W. H.	7 days before	...	+++	2000	600	2600
		21 days after	Yellow	+	1400	0	1400
27	152671 H. L.	20 days before	Dark brown	...	6000	4000	10000
		14 days before	Dark brown	...	5000	1000	6000
		21 days after	...	...	800	0	800
29	154493 D. D. H.	9 days before	Dark brown	+	3000	2000	5000
		17 days after	Yellow	...	200	0	200
30	153395 L. C. H.	9 days before	Dark brown	+++	3500	Trace	3500
		24 days after	Yellow	Trace	200	?	200
28	136512 C. G. T.	15 days before	Dark brown	+++	2200	600	2800

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DISSOCIATED JAUNDICE

By C. F. HOOVER, M.D.

AND

M. A. BLANKENHORN, M.D.

CLEVELAND

The term dissociated jaundice carries with it the inference that either the pigment or the salts of bile formed within the liver are separately shunted from the biliary path into the lymph or blood-vessels of the liver. We have succeeded thus far in showing that bile salts may possibly be shunted in this manner but we are not yet certain that bile pigment formed in the liver is separately shunted into the blood stream. This is what we would *a priori* expect when we consider the comparative facility with which the salts will pass through a dialyzing membrane, as shown by the concentrations of bile required to yield pigment and bile salts, respectively, to the dialysate when collodion sacs are employed for dialysis, and also when we consider the fact that the renal filter will yield bile salts to the urine from a lower grade of cholemia than is required for bile pigment to appear in the urine.

There have been several causes which have delayed the analysis of this very common problem in clinical pathology.

Medical men generally have been for many years misled by the erroneous interpretations of jaundice made by Stadleman and Naunyn and Minkowski, who arrived at the very definite conclusion that there can be no jaundice without the agency of the liver. According to these observers all jaundice is hepatogenic, and hematogenic jaundice does not exist. Although many clinicians have been skeptical toward the teaching that all icterus is hepatogenous, the first satisfactory experimental evidence of the truth of hemolytic

icterus, I have found, is that of Lyon-Caen,[1] 1910, and the final absolute proof of extrahepatic jaundice was given by Whipple in 1916.

Briefly stated, we have the following problems to solve in the clinical study of icterus. If pigmental cholemia is present without bile salts, the pigment may originate from the formation of bilirubin from hemoglobin within the bloodvessels as occurs in hemoglobinemia from any cause, or after complete cholemia of hepatic origin, the bile salts have been yielded to the kidney and the adsorbed bilirubin remains fixed to the plasma. The latter instance is not dissociate jaundice of hepatic origin but is merely separation of the two biliary elements by renal elimination of the bile salts. When bile salts without bile pigment are found in the plasma we are bound (by our present knowledge) to assume there exists a genuine dissociate jaundice of hepatic origin. For thus far there are no clinical or experimental evidences to show there can be an extrahepatic origin of bile salts, and in all our experimental and clinical studies we find no evidence that bile pigment can be eliminated through the kidney and bile salts retained in the plasma. If the two biliary elements are separated by renal elimination, it will always be bile pigment which will be retained in the plasma, and not bile salts. To avoid confusion in using the term "dissociation icterus" it will be advisable to employ terminology which will indicate the source of the dissociation of biliary elements in the plasma. Complete icterus will mean the presence of bile pigment and bile salts in the blood. Hemolytic icterus implies the presence of bilirubin in the blood without bile salts when bilirubin is formed extrahepatically. Hepatic dissociation icterus implies the presence of bile salts in the plasma due to bile salts being separately shunted into the blood stream. By "renal dissociation icterus" we mean the presence of bile pigment in the plasma due to separation of the biliary elements through renal filtration of bile salts and the retention of bile pigment in the plasma.

Methods. The simplest and best method of detecting bilirubin in blood plasma is Gmelin's test. Between the white coagulum

[1] Jour. de Phys. et de Path. gén. Paris, 1910, vii, 526 and 758.

and the underlying nitric acid there is a yellow granular zone. Within the white coagulum there will be seen a line more or less broad (varying with the concentration of bile in the plasma) which has a distinct blue-green color. This blue-green line will appear immediately in high concentrations of bile, but in the very low concentrations of bile in the plasma the blue-green line will not appear until after a lapse of half an hour. After the test has stood for a longer time the white coagulum will ascend in the zone of plasma but will always preserve the same thickness. The blue-green line holds its relative position in the white coagulum as the coagulum ascends, and the lower yellow zone increases in depth as the coagulum ascends.

The best method of detecting bile salts in the plasma we have found in the use of collodion sacks, which are treated with alcohol to increase their permeability. A mixture of equal parts of alcohol and water is the best medium with which to surround the collodion sack containing the plasma.

In testing for bile salts we use two or three dialyzers, each containing about 5 c.c. of plasma. After the dialyzers have stood for twelve hours, the several dialysates are concentrated, and then the concentrated dialysate is tested with Pettenkofer's method. Simply the color test and spectroscopic absorption band in the purple cannot be accepted as proof of bile salts. If no further criticism is employed, there is great danger of accepting a test as positive which is really spurious. We have adopted the plan of accepting as positive only those tests which give the characteristic color reaction to furfurol and sulphuric acid; then the spectroscopic examination of the reaction will give an absorption band in the purple. After the reaction stands for twelve hours or more a darker purple color supersedes the original pink reaction and then spectroscopic examination will reveal a disappearance of the original adsorption band in the purple and the appearance of a new, sharply defined band in the orange. The alteration in color on standing and the movement of the absorption band into the orange are essential to prove the correctness of a Pettenkofer test. The dialysate from many sera will give the original pink color and purple absorption band, but when the reaction is allowed to stand

it will not change to the pink-purple color nor will the absorption band move over to the orange. This further observation in the Pettenkofer test has saved us from making many errors in detecting bile salts in the plasma. Without this control we would have pronounced many tests as positive which were really spurious.

We find the collodion dialyzer to be a great aid in detecting bile salts. It is a very simple method and is much preferable to the old method of separating the bile salts from the proteid by repeated precipitations and filtering and washing which is practised in the Hoppe-Seyler method. Much less serum is required for the process than in the Hoppe-Seyler method in which the Pettenkofer reaction is the final test, just as we employ it with the dialysate from the plasma. The delayed spectroscopic control is applicable to the Hoppe-Seyler method of separation of the bile salts as well as in our method of separation by means of the collodion dialyzer.

We tried electrolytic dissociation to detect bile salts in plasma but met with no success. The dialyzer is much simpler and much more delicate. To procure bile salts from a solution by electrolysis requires a much higher concentration of bile salts than we find in the plasma of jaundiced patients.

We have found the collodion dialyzer and the spectroscopic control of the Pettenkofer test equally important. Both these measures have been essential to our clinical analyses of jaundice. Without a satisfactory method of detecting bile salts in plasma no progress can be made toward a study of dissociated icterus.

A review of the literature on dissociated icterus will show how the want of a satisfactory method for isolating bile salts from the plasma has hindered the progress of clinical studies of jaundice.

The Urine. Hammarstene's method is the most satisfactory means of detecting bile pigment in the urine. This is the method we always employ when any case is reported as a positive test for bile pigmentation in the urine. Bile salts in the urine have given us more trouble than in the plasma. Pettenkofer's test is not so satisfactory as Hay's sulphur test which can be inspected most satisfactorily when viewed from underneath the surface of the urine by aid of an electric lamp held between the observer's eye and specimen which is being examined. The sulphur test is very delicate

and simple and gives unequivocal results. We did not go far in studies of cholemia and choluria before we were impressed with the striking inconsistencies between cholemia and choluria. For instance, in primary anemia we have studied 13 cases and we failed to find bile pigment or bile salts in the urine of a single case, although all the patients examined had bile salts or bile pigment or both in the plasma. It is surprising to see how high a concentration of bile pigment will occur in the plasma of primary anemia without choluria. In hemolytic jaundice with infection and without infection it is also surprising to see how deeply jaundiced the plasma will become without bile pigment appearing in the urine. This is the one point which serves to distinguish obstructive jaundice from other sources of jaundice. In obstructive jaundice the bile pigment appears in the urine much more promptly and with much lower concentrations of bilirubin in the plasma than must occur in hemolytic jaundice before the urine becomes bile-stained. We find an unvarying consistency in the behavior of bilirubin toward the collodion dialyzer and toward the renal filter.

If a patient has bilirubin in his blood and none in his urine, the aqueous dialysate from his plasma will contain no bilirubin. If bilirubin occurs in both plasma and urine, the aqueous dialysate will contain bilirubin. We have had only one experience which was apparently an exception to this rule. The patient had severe hemolytic dissociated icterus, caused by streptococcus infection. The plasma was deeply stained with bilirubin, but no bilirubin could be found in the urine. The plasma dialyzed bilirubin in large amounts. The disparity in this instance was traceable to a severe disease of the renal filter, as shown both clinically and at autopsy. During life the alveolar air had a Co_2 partial pressure of 32.8 mm. Hg. The non-proteid nitrogen of the blood = 0.076 mgm. per 100 c.c. The carbonates of the blood to Van Slyke's method =26.2 mm. Hg.

It seems very reasonable in this case to ascribe the apparent exception to the rule to the impermeability of the renal filter.

When bilirubin from the plasma passes neither the renal filter nor the collodion sack, the phenomenon is due to adsorption of pigment by the plasma. We showed in one of our first clinical

studies of a case of dissociated hemolytic jaundice, due to secondary syphilis, that the renal filter was unimpaired, not only was there a want of all evidence of impaired renal function on the part of the urine and the blood, but at the same time the plasma was so deeply jaundiced as to give a very strong Gmelin's test and no bilirubin occurred in the urine, the phthalein test for renal function was perfectly normal. Unfortunately the phthalein test was neglected in the streptococcus case which gave us the single exception to consistency of behavior toward bilirubin on the part of the renal filter and the collodion sac.

The importance of adsorption of bile pigment in blood plasma is very significant in another phase of jaundice. We find the plasma deeply stained with bilirubin in some cases of primary anemia when there is not only no bilirubin in the urine but there is no trace of jaundice to the skin or sclera. This has occurred in several cases of primary anemia with complete cholemia and also in hemolytic dissociated cholemia. In several of these cases the cholemia was of such intensity that a like degree due to obstructive jaundice would invariably cause choluria and jaundice. From the pronounced disparity between cholemia, choluria and jaundice of the skin and the varying disparity in different sources for jaundice, it seems very clear that the degree of fixation of bilirubin to the plasma depends on some chemical alteration in the proteids or lipoids of the plasma.

Furthermore, we are impressed with the fact that a large amount of bile pigment and also bile salts may be in the plasma and entirely disappear from the plasma without either salts or pigment ever making their appearance in the urine. *A priori*, we would say, in view of all these facts, that the plasma has the first call on the biliary elements and holds them with considerable tenacity away from the renal filter and in some instances away from the tissues also. This adsorption of bile pigment by the plasma readily accounts for the disparity generally seen between the concentration of bilirubin in the serum of ascitic fluid and pleural fluid and the subarachnoid fluid, on the one hand, and the concentration of bile pigment in the blood plasma in cases of jaundice, and it also accounts for the fact that large amounts of bilirubin may be found in the serum

of fluid contained in the pleural cavity in cases of hemothorax without bilirubin ever appearing in the plasma of the circulatory blood. In other words, whether the bilirubin is adsorbed primarily to plasma within or without the bloodvessels, the plasma does not yield the bilirubin to the vessel wall any more readily than it is yielded to the renal filter or to the collodion sack. However, if we have a normal plasma and a normal liver, the bile pigment and bile salts are readily yielded to the liver, as is clearly shown by animal experiment. The Gmelin test for bilirubin in plasma is not sufficiently delicate to give the blue-green zone in the coagulum when bile is added to the plasma in sufficient amounts to give a visible yellow stain to the plasma. So the best method is to compare the plasma of an animal (before the injection of bile into the blood) with the plasma after the injection into the vein has been made.

The concentration of bile varies greatly. So to give us some conception of the pigment concentration of a specimen of bile and also to give some comparative idea of the quantitative value of bilirubin concentration in plasma, we record what proportion of bile or cholemic plasma must be added to a column of water one centimeter deep to give a visible yellow tinge to the water.

When we refer to a specimen of bile as having a concentration of $\frac{1}{100}$ or $\frac{1}{3000}$ and a specimen of cholemic plasma as having a value of $\frac{1}{20}$ or $\frac{1}{100}$, we mean that proportion of bile or plasma respectively must be added to a 1-centimeter column of water to give a visible color.

Experiment 1. Dog's weight, 17,000 grams.

Forty c.c. of human liver bile were injected into the brachial vein. This bile had a color value of 1 to 1000.

Estimating the circulatory blood in the dog at 1300 c.c., this would give a proportion of 30 to 1000 of bile to blood.

Oxalate plasma procured by tapping the dog's heart 5 minutes after the injection of bile had exactly the same color as the oxalate plasma procured immediately before the injection of bile. The plasma gave a negative reaction to Gmelin's test.

Huppert's test for pigment on the plasma was negative and the dialysate from the plasma gave a doubtful reaction to Pettenkofer's test for bile salts.

Five minutes after the first injection of bile 40 c.c. more of bile were injected into the vein and in another five minutes a third specimen of oxalate plasma was procured by tapping the cava. This plasma had a slight jaundiced hue and gave a positive reaction for bilirubin to Gmelin's and Huppert's tests and the dialysate gave a slight reaction for bile salts to Pettenkofer's test. The urine procured from the dog's bladder contained no biliary elements.

In previous experiments we found after intravenous injections of bile the dogs had diarrhea with intestinal hypercholia. This suggested that the reason why the dog's plasma was not stained with bile was because the liver had the first call on bile pigment and salts from the plasma when the plasma and liver were both normal.

Experiment 2. Dog's weight, 13,000 grams.

Under scopolamin and ether anesthesia the abdomen was opened and the superior mesenteric artery and the trunk of the portal vein were clamped to eliminate the biliary function of the liver. Twenty c.c. of human liver bile with a color value of 1 to 1000 were injected into the femoral vein immediately after a specimen of oxalate plasma had been taken and found to contain neither bile pigment nor bile salts. Two minutes after the 20 c.c. of bile were injected a second specimen of oxalate plasma was taken. This specimen had a slight jaundiced color and gave a positive test to Gmelin's reaction. There were neither pigment nor bile salts in the dialysate.

Seven minutes after the first injection of bile a second injection of 20 c.c. was made and two minutes thereafter a third specimen of plasma was procured, which showed a distinct increase in the yellow color and a much stronger Gmelin reaction than in the preceding specimen.

When the liver was eliminated from the circulation, the animal's plasma was stained with bile about as one would expect it to be stained were the same concentration of bile in plasma made *in vitro*.

We then performed Experiment 3, in which we proposed to eliminate the liver, inject bile into the veins and then release the clamps on the superior mesenteric artery and portal vein to see how promptly the bile would disappear from the blood.

Dog's weight, 6500 grams.

Scopolamin and ether anesthesia.

Specimen 1 of plasma was procured.

Then the abdomen was opened and the superior mesenteric artery and the portal vein were clamped. Thirty c.c. of human bile (1 to 1000), the same as in Experiments 1 and 2, were injected into the femoral vein.

Five minutes after the injection of bile, specimen 2 of oxalate plasma was procured.

Five minutes thereafter specimen 3 was taken. Then the clamps on the superior mesenteric artery and portal veins were released and the mesenteric and portal flow of blood was reëstablished.

During the procedure the pulse volume changed very little, so there could have been little change in the minute volume of blood through the heart and the hepatic artery.

Five minutes after specimen 3, specimen 4, was taken.

In five minutes more specimen 5 and in ten minutes specimen 6 of the plasma was procured.

The results of examination of the plasma gave:

Specimen 1. Clear and colorless.

Specimen 2. Clear, distinctly yellow. Gmelin's test +. Dialysate − faint color, bile salts +.

Specimen 3. Clear, yellow Gmelin +. Dialysate = faint color and bile salts +. Clamps on artery and vein released.

Specimen 4. Clear, slightly yellow, Gmelin −. Dialysate = no color, bile salts +.

Specimen 5. Clear, less yellow than 4. Gmelin −. Dialysate = color, bile salts −.

Specimen 6. Clear, very slight yellow. Gmelin −. Dialysate = no color, bile salts (?).

We then proposed to see what results a temporary obstruction of the common bile duct would give in a comparative study of the biliary elements in the plasma and in the urine. In eight trials we succeeded in getting one successful experiment in which the catgut ligature on the common duct was absorbed and the path of the common duct reëstablished, as was shown at autopsy on the

dog. The common duct of a dog was ligated with common catgut and 9 specimens of oxalate plasma were procured by heart puncture from ten to one hundred and ninety-two hours after the ligation of the duct. Each specimen of plasma was dialyzed.

Seven specimens of urine were procured from twenty to one hundred hours after the duct was ligated. The concentration value of the bile pigment in the plasma was determined.

The Pettenkofer test for bile salts was employed in the dialysate from the plasma.

In the urine Hammarstene's test was used for bile pigment and Hay's test was used for bile salts.

The results on the plasma are tabulated as follows:

	Time after ligation of common duct, hours.	Color.	Gmelin reaction.	Concentration of pigment.	Dialysate. Pigment.	Dialysate. Salts.
1	10	None	0	0	0	0
2	28	Slight	+	1.50	0	+
3	48	More yellow	+	1.60	0	+
4	72	Increase	+	1.60	0	+
5	100	Less	−+	1.50	Lost	Lost
6	120	Less	0	0	0	?
7	144	Very faint	0	0	0	?
8	168	Fainter	0	0	0	
9	192	Still perceptible	0	0	0	

The urine.	Time of ligation. hours.	Bile pigment.	Bile salts.
Spec. 1	20	0	0
Spec. 2	28	0	0
Spec. 3	36	0	+
Spec. 4	48	0	+
Spec. 5	72	0	+
Spec. 6	96	0	+
Spec. 7	100	0	+

From these results it is seen that in temporary obstruction of the common duct, although there was a marked cholemia for both pigment and salts, there was no choluria for bile pigment at any time, although bile pigment salts continued in the urine during the entire period of one hundred hours after ligation. At the same time there was marked pigment cholemia without pigment choluria. The dialysate from the plasma contained no pigment at any time, but always contained bile salts, as did the urine.

The dog had a slight icteric hue to the conjunctiva, but the icterus was not marked and would have borne a doubtful interpretation in consideration of the fact that the urine contained no bile

pigment. If only the scleral icterus and urine had been considered, the picture would have been that of a dissociate jaundice in which bile salts were dissociated from bile pigment. The examination of the plasma, however, showed the dissociation was purely a renal dissociation and not an hepatic dissociation.

Obstructive jaundice in patients may be interpreted as cases of hepatic dissociation jaundice if the urine and plasma should be examined during a period of remission.

One of our patients had gall-stones with jaundice. The plasma showed an abundance of bilirubin, 1 to 100, and positive Gmelin test. The urine also contained bile pigment, but there were no bile salts demonstrable in the plasma nor in the urine. There was no reason for suspecting a hemolytic jaundice and there were no evidences of hepatitis. The urine at the time of the observation contained only 1 per cent. of the total nitrogen in the form of ammonia and no urobilin.

The plasma and urine were examined after an acute obstruction had subsided, and on this occasion we found only the adsorbed bile pigment, which was only a survival of a complete jaundice from obstruction. Had the findings in the plasma and urine been considered apart from the clinical history and physical findings we should have interpreted the case as one of hemolytic jaundice; but when the previous removal of gall-stones and prompt recovery from jaundice and the want of any signs of hepatitis are considered, it was quite apparent we were dealing with a renal dissociation of bile salts from the bile pigment which survived in the plasma in a state of adsorption.

Another case of gall-stone lodged at the junction of the cystic and common ducts gave similar findings at one examination. When first examined the patient was icteric. The urine contained bile pigment and bile salts. The plasma was icteric, 1 to 100, and gave a positive Gmelin test. The aqueous dialysate contained both pigment and bile salts in abundance. Fifteen days later the urine contained neither bile salts nor bilirubin, and the plasma had a concentration of bile pigment of 1 to 50, and gave a positive Gmelin reaction. The aqueous dialysate from the plasma contained bilirubin, but gave only a doubtful reaction for bile salts.

The patient made a prompt recovery after the gall-stone was removed by operation. In this instance we again have the renal dissociation of salts from bile pigment in the blood. The bile pigment survived in the plasma after obstruction which originally produced complete jaundice. The following case was apparently an obstructive jaundice attending an acute gastro-duodenal inflammation.

The patient was a vigorous young man, aged twenty-one years, who came under observation on the third day of his illness, which began with nausea, vomiting, anorexia, and jaundice, with a normal temperature. On entering the hospital the liver was not enlarged nor tender. There was moderate jaundice and the stools were clay-colored. The mercuric chloride test on the stool gave only a very faint reaction after standing twelve hours. The intestinal hypocholia was very marked. The duodenal tube was passed into the duodenum and gave only very slight evidences of bile in the duodenum. Microscopically the duodenal content revealed many epithelial cells and an abundance of bacteria. The stomach secretion contained no free HCl. The urine contained an abundance of bilirubin and bile salts, but no urobilin. The oxalate plasma was jaundiced with a color concentration of 1 to 100. Gmelin's test positive. The aqueous dialysate contained much bilirubin and an abundance of bile salts. Eight days later the jaundice was much diminished. The duodenal contents showed a marked increase in the amount of bile. The urine contained no bilirubin, no bile salts nor urobilin. The oxalate plasma still showed the same concentration of bilirubin, 1 to 100. Gmelin's test strongly positive.

On this occasion alcohol and water, equal parts, were used for the dialysate and the dialysate contained both pigment and bile salts. This was an apparent exception to the rule that bilirubin in the plasma behaved toward the collodion sack as toward the kidney. But as we learned later in our experience that comparisons between the permeability of collodion sack and renal filter should be made with water as a medium around the sack and not with alcohol and water, this cannot be regarded as a fair exception to the rule that bilirubin in the plasma has the same "threshold" to renal filter and collodion sack.

Thus far we are justified in saying that in obstructive jaundice there may be cholemia without choluria and also that there may be a renal dissociation jaundice of the plasma if the blood should be examined at a suitable time after the retention of bile from the liver will have ceased.

Hemolytic Jaundice. The first patient with a clear hemolytic jaundice whom we studied was a woman who was profoundly anemic from a profuse hematemesis (ulcer). Transfusion was employed to combat the anemia. The husband acted as donor. Severe hemolysis followed the transfusion, as was shown by the chocolate-colored urine.

The following morning, twelve hours after the transfusion, the patient was observed to be icteric. The urine contained no bile pigment nor bile salts. The oxalate plasma was icteric (1 to 60). The dialysate from the plasma contained no bilirubin nor bile salts.

Another patient, a woman, who had always been in good health until an abortion was induced, which caused a streptococcus infection resulting fatally in ten days, entered the hospital with profound jaundice. On the day the plasma was examined the urine contained neither bilirubin nor bile salts.

The plasma was deeply jaundiced (1 to 275). Gmelin's test was very strongly positive.

The aqueous dialysate contained neither bilirubin nor bile salts. The dialysate from (alcohol and water) contained bilirubin but no bile salts.

A man suffering from syphilitic myocarditis attended with general anasarca developed erysipelas on both thighs where he violently scratched the skin with his finger-nails. Within a few days after the onset of the erysipelas the patient became icteric. The urine contained an abundance of bilirubin and no bile salts. The plasma was deeply stained (1 to 175). Gmelin's test positive. The dialysate from the plasma (aqueous) contained bilirubin but no bile salts.

The following case illustrates the behavior of bilirubinemia when the bilirubin is hemolytic in origin and develops extravascularly.

A young man in perfect health received a stab wound of the left thorax four days prior to his admission to the medical ward, where a large amount of blood was found in the left pleural cavity. 500 c.c. of the unclotted blood was withdrawn by paracentesis. The blood when centrifuged yielded only about 10 per cent. of its bulk in plasma. The blood did not clot on standing nor after the addition of calcium. The plasma contained a small amount of oxyhemoglobin and a very large amount of bilirubin. The plasma was not turbid. The bilirubin concentration was 1 to 450. Gmelin's test strongly positive; also Hüppert's and Hammarstene's test for bilirubin were strongly positive. The water dialysate from this plasma contained neither bilirubin nor bile salts nor urobilin.

The (water + alcohol) dialysate contained bilirubin but no bile salts nor urobilin. Blood from the patient's veins contained no bile pigment nor bile salts. The urine contained no biliary elements.

This is a very striking instance of the adsorption of bile pigment in plasma. The concentration of bilirubin was much higher in the thoracic plasma than we have found in endovascular plasma in jaundice of any kind, and in spite of the very great accumulation of bile pigment in the intrapleural plasma no bilirubin was yielded to the collodion dialyzer when water surrounded the sack.

Some unknown change in the plasma occurs, to heighten its adsorption power for bile pigment, when blood escapes into a serous cavity in a healthy person.

In another patient who acquired a bloody serous exudate in the left pleural cavity on account of carcinoma of the pleura, we found the same conditions of jaundice of the intrapleural plasma existed as in the case of traumatic hemothorax.

In none of our cases of obstructive jaundice did we find such a great disparity between pigmental cholemia and pigmental choluria as in our cases of hemolytic jaundice. When we speak of the "threshold" at which a concentration of bile pigment in the plasma will result in bile pigment appearing in the urine, however, it seems to us an error to regard this threshold as assignable to resistance offered by the renal filter to the passage of pigment.

There is a wide variation of this so-called threshold which cannot be accounted for by varying renal function. The source of this threshold lies in varying adsorption power of the plasma for bilirubin. On this basis we can account for the disparities which

exist between cholemia and choluria; and also for the varying disparities (in some patients) between the concentration of bilirubin in the blood and serous transudates, and the varying disparities between the jaundice of plasma and jaundice of the subarachnoid fluid; and finally for the varying threshold concentrations of bilirubin in the plasma toward the collodion dialyzer.

Hepatitis. Hepatic dissociation jaundice in its relation to hepatitis is not clearly depicted in our experience.

What constitutes hepatitis in many cases of acute infectious disease is not clear, and should there be only bile pigment in the plasma and urine without bile salts, the question to solve is, are we dealing with a dissociated pigmental jaundice of hepatic origin? Or are we dealing with a hemolytic jaundice which is the result of the general infection. In other words, we are dealing with evidences of blood or liver deterioration as a result of infection. The question presents itself to us in this form, because thus far we have met with no instance of bile salts dissociation in the plasma of patients suffering from sepsis of any kind, nor in patients with subacute or acute parenchymatous degeneration of the liver.

In 2 cases of pneumonia with jaundice we found only bile pigment in the plasma and no bile salts in either the plasma or urine; so there seemed very good reason for regarding the jaundice as hematogenous and not hepatogenous.

In 2 cases of acute infection we found large amounts of urobilin in the plasma along with bilirubin and bile salts. Great parenchymatous degeneration of the liver was proved in 1 of these cases at autopsy and the other patient recovered after surgical drainage of a perigastric area of infection which was due to a perforating ulcer at the pylorus.

In 2 cases of subacute hepatitis occurring in association with chronic interstitial hepatitis we were able to definitely ascribe the jaundice to a subacute hepatitis, and the plasma, and urine both contained bilirubin and bile salts.

In 1 case of chronic interstitial hepatitis, however (in which alcoholism and syphilis shared as etiological factors), the patient had an acute enlargement of the liver associated with jaundice. The patient was in the hospital three weeks. When he entered the

hospital his plasma was icteric (1 to 100) and yielded bilirubin but no bile salts to the dialysate. The urine also contained bilirubin and much urobilin, bile salts were absent and the stools contained an abundance of stercobilin. After a lapse of three weeks, during which time the jaundice diminished and all the other symptoms improved, the plasma was slightly icteric and gave bilirubin in the dialysate to alcohol-water but no bile salts.

The urine contained no bilirubin, bile salts nor urobilin. These findings we must accept as a case of dissociated pigment jaundice of hepatic origin for the following reasons:

There was a moderate jaundice (1 to 100) and pigment was liberated through the renal filter and no salts were present in either the plasma or urine. Had there been complete biliary retention in the blood from an hepatic source, both the urine and the plasma dialysate would have contained bile salts or the urine would have contained bile salts before it would have contained bilirubin. This doubt may, however, be injected into the dissociation idea, viz.: The patient had complete jaundice before entering the hospital and renal dissociation of the bile salts may have been accomplished before he came under observation, and we saw him only during a period in which the pigment was a survival of complete jaundice. That we were not dealing with hemolytic jaundice is supported by the presence of a large amount of urobilin in the urine and the fact that bilirubin was excreted in the urine when there was only moderate icterus of the plasma. That we were not dealing with a residue from obstructive jaundice is attested by the abundance of urobilin in the urine and the abundance of stercobilin in the stools.

With the exception of this last case, we have not yet seen an instance in which we could seriously consider a dissociated pigmental jaundice of hepatic origin as a probability.

Dissociated Bile Salts Jaundice of Hepatic Origin. Primary anemia affords some of the most striking characteristics of biliary elements in the blood. Of 13 cases of primary anemia whose plasma, urine, and stools, were examined for bile elements, all showed bilirubin in the plasma but 2, and bile salts were present in large amounts in the dialysate from the plasma in both these cases. In none of the 13 cases were either bilirubin or bile salts found in the urine

In primary anemia we have seen the highest concentration of bilirubin in the plasma (without perceptible icterus of the skin or scleræ) which have come under our observation. It seems in primary anemia the fixation of bilirubin in the plasma is so firm that pigment is not only never yielded to the renal filter but in some instances pigment is not yielded to the tissues when the plasma has a concentration of bilirubin as high as 1 to 75. Of these 2 cases, 1, a man, aged fifty-two years, gave a history of having been ill for fourteen months.

A few months prior to entering the hospital he had a marked lemon-yellow color to his skin. On entrance there was no trace of icterus.

Red blood cells, 2,312,000; white blood cells, 7700; hemoglobin, 70 per cent.; color index, 1.5.

The differential count: polymorphonuclears, 67 per cent.; small mononuclears, 23 per cent.; large mononuclears, 7 per cent.; transitionals, 3 per cent.

The neurological signs were very marked. There was a loss of both patellar and ankle reflexes. Impairment of the vibratory sense in upper and lower extremities and acro-ataxia and proximo-ataxia in both upper and lower extremities. The plasma was colorless and the dialysate gave a reaction to the Pettenkofer test which was strongly positive, not only changed from cherry red to purple on standing twelve hours, but the spectroscopic examination showed the movement of the band on standing from the purple into the orange. This patient was an instance of primary anemia who had formerly pigment as well as salts in his blood, but during the period he was under our observation his blood contained an abundance of bile salts without pigment.

The other case of primary anemia which yielded salts from the plasma without pigment was one in which there may be some doubt about the primary anemia. The diagnosis of primary anemia was made from the history of former anemia and the characteristic neurological signs associated with degeneration of the posterior and lateral columns of the cord, with a normal cell count and negative Wassermann reaction on the spinal fluid. We regarded this patient as one who had recovered from his anemia with per-

sistence of the neurological symptoms. However this may be, the point of interest in this patient lay in the fact that bile salts were present in abundance in his plasma, as shown from the Pettenkofer test with spectroscopic confirmation, and no bile pigment was found in the plasma nor in the urine, and no bile salts were found in the urine.

A very similar condition was found in 1 case of lead poisoning which occurred in a house painter who had been occupied with color mixing and painting for a period of two years prior to his admission to the hospital. The man had a very characteristic lead line on the gums and gastro-intestinal symptoms. The red cells = 4,600,000.

Hemoglobin, 70 per cent. (Talquist). There was none of the characteristic stippling of the red cells and no hemorrhages from mucosæ as in the skin or retinæ. The plasma was slightly stained with bilirubin but not sufficient to give the Gmelin test. The tests for bile salts in the plasma were quite the same as in the cases of pigment anemia above described. Thus far we can say that in primary anemia and lead poisoning we have found three instances of dissociated bile salts retention from the liver.

Summary. 1. The collodion sack dialyzer is the most delicate and satisfactory method of isolating bile salts from the plasma.

2. That many of the cases of supposed dissociated jaundice heretofore reported are not phenomena of retention from the liver but they are instances of renal dissociation of what originally were cases of complete jaundice.

3. Renal dissociation always leaves the bile pigment as survivor in the plasma.

4. Pigmental dissocated jaundice can originate only from a hemolytic source.

5. Bile salts dissociation may occur in retention in the blood from the liver, but the correctness of this interpretation awaits the confirmation of the doctrine that bile salts cannot have an extrahepatic origin.

THE BILE CONTENT OF THE BLOOD IN PERNICIOUS ANEMIA

By M. A. BLANKENHORN, M.D.
CLEVELAND, OHIO

(By Invitation)

Although jaundice is one of the commonest symptoms of pernicious anemia, and a symptom which is intimately associated with the most distinct pathological process in pernicious anemia, namely, hemolysis, it has never aroused much curiosity. The presence of bile in the blood in any condition has not been extensively studied; in fact, this field is so wanting in methods that little is known of even the normal bile content of the blood, and jaundice of the plasma has been given no value in any condition. Rather extensive chemical studies of the blood in pernicious anemia have been made, especially by Erben,[1] Rumpf,[2] and von Jaksch,[3] but these and others make no mention of the biliary elements, save that the amounts of cholesterin and lecithin are diminished, a finding that is common to many chronic diseases, especially when starvation is a factor. Sylabe[4] found bilirubin in the blood in 8 cases of pernicious anemia. Wilbur and Addis[5] in their observations on urobilin in the plasma did not find that substance present in pernicious anemia.

Methods. Oxalated plasma was used in every case. The Gmelin test for bilirubin was used in testing for bile pigment, which gives the well-known blue-green color with nitric acid. This method was applied to the plasma by Gilbert,[6] who arrived at conclusions as to the normal bilirubin content of the human plasma. The Gmelin test on the plasma is made by putting nitric acid under

the plasma in a test-tube with a small pipette. A white coagulum is formed at once at the junction, which soon develops into a white layer of certain thickness, and remains fairly constant as the acid dissolves the coagulum at the lower border and forms it at the upper, thus ascending through the plasma. The blue-green color develops in a line at the center of the white zone, and remains in this relative position as long as there is any white zone. When bilirubin is present in small amounts the blue color may be as long as a half-hour in appearing. Since the white coagulum forms a good background on which to see the blue line, the tests are very satisfactory and give unequivocal results.

Just what minimum amount of bilirubin gives this test we cannot say, but ordinary gall-bladder bile can be diluted 600 times in colorless plasma and still give this test. Gall-bladder bile contains about 2 per cent. pigment, chiefly bilirubin, so approximately the test will show one part in thirty thousand. It is therefore quite certain that a plasma may be visibly bile-stained and still not give the Gmelin test, for ordinary gall-bladder bile may be diluted 5000 times and the yellow color be just perceptible in a column 1 cm. deep, and since only 2 per cent. of bile is bilirubin, we conclude that bilirubin can be diluted 250,000 times and still be just visible, making the inspection of the plasma a test much more sensitive than the Gmelin.

We have found no way of cencentrating small amounts of pigment, nor do we have any very satisfactory quantitative method for measuring the bilirubin. We have accepted the staining of the plasma as a measure of the bilirubin content, for we have found no other yellow substance in our plasmas, and do find the intensity of Gmelin's test proportional to the degree of yellow staining.

For our records we have been expressing the bilirubin content of the blood by the dilution that is required to diminish the staining to the point where it is just perceptible in a column 1 cm. deep. Plasma to be thus measured must be obtained free from hemolysis. In diluting the plasma with distilled water a faint precipitate of globulin sometimes appears in suspension, which can be put in solution by a drop of ammonium hydrate. The end point of the dilution, that is, when the yellow color is just perceptible, is found

by comparing the solution in a small test-tube with a similar column of distilled water. To facilitate reading, the tubes are held parallel and observation made down the length of the tube, and a device which serves to bring the two columns to still more equal terms is to immerse the ends of the tubes in an inch or two of water in an evaporating dish. This cuts out all reflecting surfaces and gives a white background. While this by no means serves to make quantitative estimates of bilirubin in the blood, it does give us a method for comparing and recording the jaundice of the plasma within about a 10 per cent. error. By this method we have found plasmas the staining of which we have estimated from 10 up to 275, and find that all at 20 or over give a positive Gmelin test.

For urobilin we have depended on the Ehrlich aldehyde test on the oxalate plasma directly. Most of the blood protein is first precipitated by 1 or 2 volumes of saturated alcoholic solution of zinc acetate and centrifuging; 5 to 10 drops of the aldehyde reagent are added and a pink to dark red color develops, which gives the characteristic spectra if urobilin or urobilinogen are present. While negative results by this method are not always acceptable, we have found the test positive in three instances and always strongly positive.

For the detection of the bile salts we have depended on the Pettenkofer test, but have no methods for measurements. The Pettenkofer test is not specific for bile salts or for any group, and therefore all its results must be carefully criticized. On account of its lack of specificity the Pettenkofer reaction appears very seldom in the literature (other than biochemical). Pettenkofer in his original description named forty substances that give it. Of those that occur in the blood and are known to give it are cholesterin and lecithin, also many alcohols, fatty acids, and aromatic substances. The absorption spectra of the Pettenkofer test is said to be more nearly specific than the color test alone, so we have controlled all our color tests by the spectroscopic examination in addition.

The Pettenkofer test cannot be applied directly to the blood or blood plasma, but the bile salts must be separated from the blood proteins and be relatively free from lecithin and cholesterin. This

has been done by precipitating the salts with basic lead acetate and ammonium, after the proteins have been removed with large amounts of alcohol—the Hoppe-Seyler method—a process which is long and tedious, requiring much time and many manipulations. But we have found we can obtain the salts relatively free by dialyzing the plasma through collodion sacks into water or water and alcohol. In investigating the jaundice in other than pernicious anemia we have examined the same specimen by both methods and found the results quite consistent.

Our usual method has been in all cases to separate the salts from the plasma by dialysis through collodion sacks into water or water and alcohol; 5 c.c. of plasma are dialyzed into 5 c.c. of water or equal parts of water and alcohol, and two or three such dialyzers are allowed to stand overnight. The collected dialysate is then concentrated and the Pettenkofer test applied, and the spectroscopic examination made if any color develops. For the test, 2 c.c. of concentrated dialysate is placed in a small flask with two or three drops of a 1 to 1000 aqueous solution of furfurol, and 2 c.c. of concentrated sulphuric acid are added drop by drop from a pipette; but the contents of the flask are kept at 60° C. by immersing the flask in a bath at 60° and keeping the mixture agitated. When the acid is added too rapidly, a dark reddish-brown color appears from the charring action of the acid. If the temperature remains much below 60°, the color fails to develop or appears very faint.

We know that bile salts dialyze very rapidly into water or dilute alcohol from human fistula or bladder bile and from aqueous solutions of pure bile salts. Lecithin or cholesterin being insoluble in water and poorly soluble in dilute alcohol, we think are not dialyzed under these conditions, at least we have not been able to find them. Also on evaporating the dialysate to dryness and extracting with ether—in which lecithin and cholesterin are soluble —the substance that gives the Pettenkofer reaction is not removed. We have, furthermore, precipitated the bile salts from plasma by lead acetate and ammonia (by the Hoppe-Seyler method) in 4 cases of pernicious anemia in which strong tests were found after dialysis and obtained the salts in both instances. The spectrum of a Pettenkofer test for bile salts obtained from human bladder and

fistula bile by dialysis and by the Hoppe-Seyler method shows a wide absorption band in the blue when the test is first made and is of a cherry-red color. Later as the cherry turns to purple the band in the blue fades and a smaller band develops in the orange (near D. between D. and C.). In a strong reaction both may be visible at once, but in weaker reactions the band in the blue usually fades before the other appears. This same spectrum is given by bile salts dialyzed from the plasma as well as by those precipitated by the Hoppe-Seyler method. Numerous plasmas dialyze salts into water that give the Pettenkofer test, *i. e.*, the cherry-red or pink color turning to purple, but not in concentration sufficient to allow the positive identification of the absorption bands. So we have been obliged to accept as positive in many instances reactions that give the colors but not the spectra.

Whether in every instance in which we have found a positive Pettenkofer test bile salts are present, we cannot bring unchallengeable evidence, but we have found such tests in sufficient blood plasmas associated with definite diseases of the liver and have found it wanting from sufficient normal plasmas, so that we are satisfied that it is not a property of normal blood. We have not found the Pettenkofer reaction to be adaptable to quantitative measurements either colorimetrically or spectroscopically, but do find that there is a distinct variability in the intensity of the color reaction as well as in the definition of the absorption bands. This is sufficiently clear. Therefore we can classify these tests as, plus, double plus, and triple plus.

By these methods we have examined the plasma of 13 patients in whom a diagnosis of pernicious anemia had been made. That is, we have tried the Gmelin reaction; measured the staining of the plasma; tested for urobilin; dialyzed and examined the dialysate for bilirubin and tested it for bile salts with the Pettenkofer and spectroscopic tests. The results of this investigation are summarized in Table I. In this table also are certain other observations that are immediately concerned, namely, the blood findings relative to the anemia; the skin jaundice; the biliary elements in the urine, and the total urobilin in the stool. On the urine we have used the Hammarstene-Salkowski test for the bile pigments; the Hay test

TABLE I

Name.	Age.	Red blood cells.	Hemoglobin (Talquist).	Color index.	Skin.		Blood.			Urine.			Stool, urobilin.	Loss of strength.	Neurological symptoms.			
					Jaundice.	History of jaundice.	Jaundice of the plasma.	Gmelin's test.	Dialysis.	Bile pigment.	Bile salts.	Urobilin.			Vibration test.	Paresthesias.	Acro-ataxia.	Proximo-ataxia.
									Salts.	Pigment.								
L. H.	60	1,032,000	30	1.5	+	+	20	+	0	0	0	0	Increased	Marked	0	+	+	0
(2 mos. later)	..	3,500,000	70	1.0	+	+	15	0	+	0	0	0	.....	Less marked	0	0	0	0
M. C.	52	1,200,000	40	1.7	+	+	60	+	+	0	0	+	Increased	Very great	ǂ	+	0	0
B. S.	63	3,300,000	70	1.05	+	0	..	+	+	0	0	+	.....	Marked	ǂ	+	+	0
(3 mos. later)	..	3,300,000	70	1.05	+	0	15	+	+	0	0	+	.....	Marked	+	+	+	0
S. H.	57	2,277,000	60	1.3	0	0	20	+	+	0	0	+	Increased	Marked	+	+	+	0
U. A.	52	2,312,000	70	1.5	0	0	0	+	+	0	0	+	.....	Slight	+	+	+	0
C. A.	60	2,256,000	75	1.7	0	0	50	+	+	0	0	+	.....	Slight	+	+	+	0
F. C.	64	1,400,000	40	1.4	+	+	150	+	+	0	0	+	Much increased	Great	0	0	0	0
M. B.	48	3,824,000	80	1.05	0	0	15	0	?	0	0	+	Slightly increased	No	ǂ	+	0	0
L. C.	42	3,400,000	70	1.0	0	0	75	+	?	0	0	+	.....	No	ǂ	+	0	0
E. B.	39	1,206,000	70	2.9	0	0	50	+	+	0	0	+	Increased	Very great	0	+	0	0
J. W.	56	1,168,000	40	1.7	+	0	70	+	+	0	0	+	Greatly increased	Very great	+	+	+	0
(1 mo. later)	..	1,944,000	65	1.7	0	+	20	0	+	0	0	+	Increased	Marked	+	+	0	0
L. Y.	45	3,734,000	75	1.07	0	0	50	+	+	0	0	0	.....	Slight	0	+	+	+
H. K.	47	3,870,000	85	1.1	+	0	0	0	+	0	0	0	.....	Very great	ǂ	+	+	0

for the bile salts, and the Ehrlich aldehyde test for urobilin. On the stool we have used the Wilbur and Addis method of measuring the total daily urobilin excretion. And to correlate with the clinical side, the table is made to include an index of the two most significant symptoms in the cases studied, *i. e.*, the loss of strength and the nerve disturbances. In the latter the determination of the ataxias is made by the plan demonstrated by Hoover in 1914, acro-ataxia being an ataxia of the fingers and toes and proximo-ataxia, an ataxia of the iliofemoral or of the thoracicohumeral group of muscles.

Results. Bilirubin: In brief the table shows that out of the 13 cases, in 10 there was found bilirubin in amounts sufficient to give a positive Gmelin test. In 1 of the remaining 3, the plasma was visibly jaundiced, but not deeply enough to give a test. The bilirubin showed no constancy in amount, the staining varying in intensity from 10 to 150, according to the method above described. In all of these cases there was no bilirubin in the urine. Four of the 13 plasmas contained bilirubin in concentration, above the "threshold" for bilirubin in the kidney, as compared with certain other types of jaundice, which always give choluria at a certain concentration, namely, 60 or over. The bilirubin did not dialyze from the plasma of any case into water through collodion sacks. Of the 13 cases showing staining of the plasma, 7 were visibly jaundiced in the scleræ, of the remaining 6 only 1 gave a history of ever being yellow. The cases showing the highest concentration of bilirubin showed the most marked evidence of rapid blood destruction, namely, increased output of urobilin in stool and urine, loss of strength from anemia, also the highest color index.

Urobilin: Urobilin was not found in the plasma of any, although urobilin occurred in the urine of all save 1, this 1 being a case which showed absolutely no staining of the plasma.

Salts: A positive Pettenkofer test was found in 10 out of 13 plasmas. There was no direct correspondence between the presence of salts or the amount of salts and the amount of bilirubin in the plasma. One plasma, with a jaundice of 75, gave a doubtful Pettenkofer, while 2 others with absolutely no staining of the plasma, gave a strong Pettenkofer. Bile salts were found in the

urine of none of the cases. There was no apparent relation between the amount of bile salts and the blood destruction or color index. It was observed, however, that the cases giving the strongest Pettenkofer, hence highest concentration of salts, showed the most marked nerve lesions—in fact in 3 such cases the nerve lesions caused all the symptoms of the disease.

By these same methods we have examined the plasma of a series of patients selected on account of suspected liver disease, infections, anemias, etc., as well as a few normals. Table II summarizes 8 of these cases, 7 being secondary anemias from various causes, and 1 case of Banti's disease. Of the 7 anemia cases none showed any staining of the plasma, although 2 of them were described by the ward physician as appearing jaundiced at the time the specimens were taken. One of the anemia cases had bile salts in the plasma. The case of Banti's disease looked jaundiced and had both bile pigments and salts in the plasma but neither in the urine.

TABLE II

Name.	Age.	Diagnosis.	Red blood cells.	Hemoglobin (Talquist).	Color index.	Skin.		Blood.				Urine.			Stl.
										Dialysis.					
						Jaundice.	History of jaundice.	Jaundice of plasma.	Gmelin's test.	Bile pigment.	Bile salts.	Bile pigment.	Bile salts.	Urobilin.	Urobilin.
A. B.	..	Hemorrhoids	2,144,000	20	47	+	0	0	0	0	0	0	0	0	
J. S.	..	Chronic bismuth poisoning	1,500,000	30	1	0	0	0	0	0	0	0	0	0	
P. G.	..	Splenomegaly	3,144,000	40	.65	+	+	15	0	0	0	0	0		
A. S.	..	Banti's disease	5,100,000	85	.85	+	+	40	+	0	+	0	0		
J. S.	..	Lead poisoning	4,640,000	70	.7	0	0	0	0	0	+	0	0	0	
L. Z.	..	Incomplete abortion	3,064,000	45	.7	0	0	0	0	0	0	0	0	0	
J. L.	..	Nephritis	2,880,000	50	.9	0	0	10	0	0	0	0	0	0	
W. H.	..	Carcinoma, stomach	4,000,000	70	.9	0	0	10	0	0	0	0	0	0	

In a group of 40 or thereabouts, selected on account of liver disease (principally alcoholic and infectious cirrhosis); disease of the bile ducts; general infections with jaundice and jaundice after transfusion, we have found bile pigment and bile salts in the plasma in varying amounts, and in varying relations to each other and to choluria. The interpretation of the blood jaundice in the various

conditions is yet to be worked out. A few main points are clear, viz., that jaundice of the sclera or skin is, of course, always associated with jaundice of the plasma, but the converse is not true, for we have frequently been surprised by obtaining a distinctly jaundiced plasma from a patient who has no suggestion of jaundice of the skin. Also in the main the presence of bile salts in the blood is associated with some disease of the liver, which is in accord with the idea most commonly held—that bile salts are formed only in the liver. In the plasma of 10 normal individuals we have found no bile pigment or bile salts.

From our experience with jaundice of the plasma in the various diseases of the liver, and the frequent appearance of bile salts in the blood in pernicious anemia, we can venture one interpretation of our findings in the 13 cases tabulated, namely, that the jaundice is hepatic in origin. From the fact that the bile pigment in these 13 cases was not found in the urine, and furthermore does not dialyze through collodion membranes into water, we conclude that the pigment is fixed to the plasma, perhaps chemically. This fixation does not seem to depend on the intensity or duration of the jaundice. Why the bile salts are diffusible from the plasma through collodion membranes and do not appear in the urine, we have no theory.

What diagnostic value may be attached to the findings of bile pigment and bile salts in the plasma remains to be seen, but it is quite apparent that jaundice can be estimated with more certainty from observations of the plasma than from observations of the skin and scleræ. In the anemias, especially, a faint degree of jaundice, such as occurs in pernicious anemia, is frequently a matter of uncertainty, for the pallor exaggerates the normal pigmentation of the skin; the so-called "lemon-yellow" skin is often a much-disputed symptom. The large amount of bilirubin in the plasma in some cases increases the difficulties met in obtaining estimations of hemoglobin by the Talquist or Sahli method, for the adventitious yellow color prevents an accurate reading, and tends to make the results too high. The diagnostic value of the presence of bile salts in the blood also is not very clear, but we are inclined to accept such a finding as direct evidence of pernicious anemia in those cases

where the anemia is a minor feature, although neurological signs and symptoms are the main features of the disease. In the diagnosis of pernicious anemia we have relied principally upon finding a marked anemia with a high color index associated in early cases with paresthesias of the extremities, and other evidence of degeneration of peripheral nerves, and with degeneration of the columns of the spinal cord in more advanced cases. In defense of so large a series of pernicious anemia patients in ten months in a clinic such as is maintained at Lakeside Hospital, we can explain that most of them came by selection from a large private consulting practice.

As a method of prognosis the measure of the jaundice of the plasma may be of considerable help, for we have found in the 2 cases that we were able to observe after a few months' interval that the jaundice had diminished with the improvement. Also that the patients kept on the ward and treated show a decrease in blood jaundice as they get relief from symptoms—the decrease is usually proportional to the increase in red cells.

Summary: Bile pigment is frequently found in the blood in pernicious anemia, and is the cause of the jaundice. The pigment is in some way fixed to the plasma and therefore does not appear in the urine. The presence of bile pigment in the blood is not always betrayed by jaundice. Bile salts are frequently found in the blood, alone or associated with bile pigment. The jaundice in pernicious anemia is hepatic in origin.

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DISCUSSION ON THE PAPERS OF DRS. GIFFIN, HOOVER AND BLANKENHORN, AND BLANKENHORN

Dr. L. G. Rowntree, Minneapolis, emphasized the great value of Schneider's work which had been alluded to by Dr. Giffin. Bile in per-

nicious anemia is ordinarily very dark; it differs from the bile in other forms of anemia in appearance and in its content of bilirubin, urobilin and urobilinogen. Schneider is now finding the biliary changes typical of pernicious anemia in some cases of atrophic cirrhosis of the liver. Did Dr. Giffin's work include any cases of acute aplastic anemia?

Dr. R. C. Cabot, Boston, said that the age of splenectomized pernicious anemia patients has a potent influence on the outcome. Transfusion after splenectomy has a more lasting good effect than when done with spleen still in place. Had Dr. Giffin noticed any great tendency to thrombosis following splenectomy?

So far as the usefulness of splenectomy in pernicious anemia is concerned, he expects to have his spleen removed whenever he acquires pernicious anemia.

Dr. G. H. Whipple, San Francisco, inquired if Dr. Blankenhorn had tested the blood plasma with Huppert's test. This is a much more convincing test than those mentioned in the paper. In our laboratory it has been noted that the blood of pernicious anemia often yields "half-baked" pigments which may easily be mistaken for bilirubin. The finding of bile in the plasma with no bile in the urine should be very carefully checked. If Dr. Blankenhorn had found a really satisfactory test for bile salts, he is to be congratulated.

Dr. C. F. Hoover, Cleveland, said that Dr. Blankenhorn had spoken of the use of Pettenkofer's test. This test was controlled by the use of the spectroscope: in the presence of bile pigments there is a characteristic movement of absorption bands; no tests in the work reported had been accepted unless this movement of the absorption bands was noted.

The separation of bile salts from plasma may be easily and quickly done by collodion sack dialysis. This was the most satisfactory method found.

Many of the cases of so-called dissociation jaundice were really cases of renal dissociation of what was originally a complete jaundice.

Dr. M. A. Blankenhorn, Cleveland, said that there is no more delicate test for bile pigments than Gmelin's; all the others had been thoroughly tried and compared. He accepted Dr. Whipple's congratulations on the finding of a satisfactory test for bile pigments with the same reserve with which the congratulations were offered; those employed were the best that have been devised to the present time.

THE EFFECTS OF EXPOSURE TO COLD UPON EXPERIMENTAL INFECTION OF THE RESPIRATORY TRACT

By JAMES ALEXANDER MILLER, M.D.

AND

WILLIS C. NOBLE, Ph.D.

NEW YORK

Exposure to cold has long been considered an important factor in the incidence of many respiratory diseases. Even with our increasing knowledge of the predominating role of bacterial infection, the belief is still very general among clinicians that chilling of the body exerts a predisposing influence of considerable importance.

In reviewing the general subject of the effect of atmospheric conditions upon bodily health and efficiency, the New York State Ventilation Commission was impressed with the comparative lack of accurate data concerning the physiological effect of low temperature, the majority of recent observers having interested themselves mainly with the study of various degrees of heat.

Experimental studies of the influence of cold as well as of heat have therefore formed a part of the work of the commission for the past two years. The experiments here reported constitute a portion of these studies.

Experimental Work. The organism chosen for inoculation was the Bacillus bovisepticus, or "snuffles" bacillus, which belongs to the hemorrhagic septicemia group, and is pathogenic for the rabbit. It is a small, plump bacillus with a marked tendency to bipolar staining, particularly in blood smears made from animals dying

from infection caused by it. The disease produced under natural conditions is generally a true septicemia, but in many cases is localized in the upper respiratory passages, when it is commonly known as "snuffles." This condition is characterized by a typical discharge of yellowish mucus from the nostrils, and may terminate in recovery or in a fatal pneumonia with or without general septicemia.

It will thus be seen that the conditions produced in the rabbit by this bacillus are similar to some of the respiratory infections in man, such as those caused by the pneumococcus and influenza bacillus. The organism was selected for use in our work because of this fact and because of the relative difficulties which have attended previous experiments with acute respiratory infections, particularly the pneumococcus.

Experiment 1. This experiment was conducted partly during the late winter months of 1915 and partly during the similar cold months of 1916. Thirty-seven experimental rabbits were used in thirteen separate series, of from 2 to 4 animals, each with an equal number of controls.

The experimental rabbits were kept in an incubator at warm temperatures for periods varying from one day to one week. In eleven series this temperature was between 85° to 90° F., and in two it varied from 70° to 76° and 63° to 78° respectively, being, however, at the higher level most of the time. The animals were then inoculated by spraying the nasal mucous membrane or the throat with a small amount of the live culture of the Bacillus bovisepticus, emulsified in salt solution. After inoculation they were immediately chilled by exposing them to the outside weather for periods varying from one-half to three hours and at a temperature of 56° F. or below, in one case 20° F. In the majority of the experiments the fur of the animals were wet with water at about body temperature to facilitate chilling upon exposure. The details of temperature, time of exposure, method of inoculation, etc., are shown in the tables.

The control animals, also 37 in number, were kept constantly at a temperature of 65° to 70° F., and were inoculated at the same time and in the same manner as the experimental animals of the corresponding series. None of these were wet.

TABLE I

Series.	Heated and exposed.			Controls kept at room temperature 65° to 70° F.		
	Number of rabbits.	Reactions.		Number of rabbits.	Reactions.	
		Died.	Sick.		Died.	Sick.
1	4 24 hrs. at 87° F. chilled to 45° F.; 1 hr. exposure; 2 fur wet, 2 fur dry; 2 nose, and 2 throat	2 Pneumonia; 1 wet, 1 dry, 48 hours	1 General reaction; recovered; could hardly move; no appetite	4 ...	0 ...	1 General reaction; recovered.
2	2 1 week at 85° F. to 89° F.; chilled to 40° F.; 1¼ hour exposure; fur dry; 1 nose and 1 throat	0 ...	1 Snuffles; recovered.	2	0	0
3	2 1 week at 85° F. to 89° F. chilled to 38° F.; 3 hrs. exposure; fur dry; 1 nose and 1 throat	0 ...	1 Snuffles; recovered	2 ...	1 Pneumonia; one week.	0
4	4 1 week at 85° F. to 90° F.; chilled to 38° F.; 1½ hrs. exposure; fur dry; 2 nose, and 2 throat	0	0	4	0	0
5	4 1 week at 85° F. to 90° F.; chilled to 56° F.; 1 hr. exposure; fur dry; 2 nose, and 2 throat	0	0	4	0	0
6	4 1 week at 85° F. to 90° F.; chilled to 20° F.; ½ hr. exposure; fur dry; 2 nose and 2 throat	1 Snuffles; septicemia; death in 10 days	0	4	0	0
7	4 1 week at 85° F. to 89° F.; chilled to 45°F.; 2 hrs. exposure; all dry fur; 2 nose and 2 throat	0 ...	1 Snuffles; recovered	4 ...	0 ...	1 Snuffles; recovered.
8	3 1 week at 85° F. to 90° F.; chilled to 40° F.; 3 wet fur	0 ...	2 Snuffles; recovered.	3	0	0

TABLE I—Continued

Series.	Heated and exposed.			Controls kept at room temperature 65° to 70° F.		
	Number of rabbits.	Reactions.		Number of rabbits.	Reactions.	
		Died.	Sick.		Died.	Sick.
9	2 3 days at 70° F. to 76° F.; chilled to 25° F.; ½ hr. exposure; all with wet fur; 1 nose, and 1 throat	1 Pneumonia. Death in 2 days; inoculated in throat	1 Snuffles; inoculated in nose; recovered.	2	2	0
10	2 3 days at 85° F. to 93° F.; chilled to 52° F.; ½ hr. exposure; all with wet fur; 1 inoculated in nose and 1 in throat	1 Pneumonia. Death in 11 days; inoculated in nose	0	2	0	0
11	2 24 hrs. at 82° F. to 87° F.; chilled to 27° F.; exposure ½ hour; wet fur; inoculated 1 in nose, and 1 in throat	0 ...	0 ...	2 ...	0 ...	1 Snuffles; inoculated in nose; recovered.
12	2 24 hrs. at 85° F. to 90° F.; fur wet; exposed to 31° F. for ½ hr.; inoculated 1 in nose and 1 in throat	0 ...	1 Snuffles; severe reaction; recovered; inoculated in nose	2 ...	0 ...	2 Snuffles; mild reaction; recovered.
13	2 4 days at 63° F. to 78° F.; fur wet; exposed to 32° F. for ½ hr.; inoculated 1 in nose and 1 in throat	1 Pneumonia; inoculated in throat; death in 3 days	1 Snuffles; inoculated in nose; recovered	2	0	1 Snuffles; inoculated in nose; recovered.
Total	37	6	9	37	3	6

Results. Of the experimental rabbits, 5 died of pneumonia, 1 of general septicemia, while 9 were made ill, but recovered. Of the controls 3 died and 6 were infected but recovered. In every case when death resulted the animal was autopsied, the character of the lesions noted, and the specific organism isolated from the heart's blood.

It will thus be seen that of the experimental animals 15, or 40 per cent., reacted and only 9, or 24 per cent., of the controls. It is also worthy of note that this difference in reaction between the experimental and the control groups was quite harmoniously distributed throughout the entire thirteen series of experiments. In only two series (Nos. 11 and 12), did the number of reactions in the control group exceed that of the experimental animals.

The details of this experiment are shown in Table I.

Experiment II. At the conclusion of our previous experiment it seemed desirable to note the effect of reversing the conditions, that is, to determine the result of a change from a cold to a hot temperature. It was only possible to conduct two series in this experiment. Four animals were kept at outdoor temperature for two days, and after inoculation, as in the previous experiment, were placed in an incubator at 78° to 80° F. for from six to twelve days. A similar number of controls, inoculated in the same way, were kept constantly at room temperature of 65° to 70° F.

Results. Of the experimental animals all reacted, of which one died. Of the controls only two reacted, one of which also died.

For detailed description see Table II.

TABLE II

Series.	Kept cold in the open; then heated in the incubator.			Controls kept at room temperature 65° to 70° F.		
	Number of rabbits.	Reactions.		Number of rabbits.	Reactions.	
		Died.	Sick.		Died.	Sick.
14	2 2 days at 41° F. then kept at 80° F. for 12 days; inoculated 1 in nose and 1 in throat	0 ...	2 Snuffles; 1 reacted in 4 days; inoculated in nose; 1 reacted in 6 days; inoculated in throat	2 ...	0 ...	1 Reacted in 12 days; inoculated in nose.
15	2 2 days at 35° F. to 40° F., then kept at 78° F. for 6 days	1 Pneumonia; inoculated in throat	1 Snuffles; inoculated in nose	2	1 Pneumonia; inoculated in throat	0
Total	4	1	3	4	1	1

Experiment III. From the results obtained in the two foregoing experiments it seemed desirable to attempt one further experiment in which three modifications of the experimental conditions were considered together.

1. A change from outside temperature (59° F.) to incubator temperature (80° F.) (Series 16).

2. A change from room temperature (65° to 70° F.) to incubator temperature (80° F.) and then down to a low temperature (50° to 60° F.) and from that back to room temperature (65° to 70° F.) (Series 17).

3. A repetition of the conditions of Experiment 1, namely, chilling from a high temperature (80° F.) to a low one (57° F.) (Series 18). All three series of this experiment were carried on simultaneously with 2 animals in each series and with one set of 2 control animals which were kept continuously at room temperature (65° to 70° F.).

Results. In series 16 a change from low to high temperature, both animals died of pneumonia.

In Series 17, with several changes from room temperature, to high, then to low and back to room temperature, both animals reacted, of which one died of pneumonia.

In Series 18, a change from high to low temperature, only one animal reacted slightly with snuffles.

Neither of the two controls reacted.

Table III shows these results in detail.

We wish to acknowledge our obligation to Mr. I. Weinstein for valuable assistance in conducting the details of the animal work in some of the experiments.

Discussion. Other experimental studies of respiratory disease have been quite numerous, but few of these deal directly with the associated problem of the effect of chill with which we are at present concerned.

Lipari,[1] in 1888, reports the results of intratracheal injections of pneumonic sputum in guinea-pigs and rabbits which, after exercise by running, were chilled either by cold baths at 3° C. or by the application of ether to the skin after shaving the animals. Of 8 chilled animals 6 died, while only 2 of 12 controls were infected.

TABLE III

Experimental.										Controls kept at 65° to 70° F.		
Series 16.			Series 17.			Series 18.						
Kept cold (59° F. for 48 hrs.); inoculated and kept at 80° F., 1 in nose and 1 in throat			Kept at 65° to 70° F. for 48 hours; inoculated and kept at 80° F. for 24 hrs.; in open for 4 days (50° to 60° F.), then at room temperature (65° to 70° F.)			Incubated, 80° F. for 2 days; inoculated, fur wet and exposed at 57° F. for 20 minutes, then kept at 65° to 70° F.						
No. of rabbits.	Died.	Reacted.	No. of rabbits.	Died.	Reacted.	No. of rabbits.	Died.	Reacted.		No. of rabbits.	Died.	Reacted.
2	2 Pneumonia	0	2	1 Inoculated in nose; died from pneumonia in 6 days	1 Inoculated in throat; mild attack of snuffles in 7 days	2	0	1 Inoculated in throat; snuffles in 3 days.		2	0	0

Lode,[2] in 1897, shaved guinea-pigs over one-half to two-thirds of the body, exposed them to heat 37° C. for one-half hour, and then chilled them in draughts at open windows. Using Buchner's apparatus, he exposed them to the spray of culture of Friedländer's bacillus. Of 11 chilled animals 7 died, while only 3 of 11 controls succumbed. In a similar inhalation experiment with tubercle bacilli, of 5 chilled animals all died, but only 2 of 4 controls. He also used Friedländer's bacillus, cholera and Staphylococcus aureus subcutaneously in his series, as well as a few chickens and rats with anthrax. Altogether, including both inhalation and subcutaneous methods, he reports that 46 of 54 chilled animals (80 per cent.) died and only 9 of 45 controls (20 per cent.).

Pasteur's[3] experiments upon chickens made susceptible to anthrax by partial immersion in cold water are well known, but these as well as others not dealing with direct respiratory infection need not be considered here.

Chodounsky,[4] who has covered the whole field of the relation between exposure to cold and disease perhaps more extensively than any writer, comes to the very emphatic conclusion that such exposure plays no part in determining the incidence of any of the various

so-called "cold diseases." As a part of his vigorous contention he offers considerable experimental evidence of his own concerning respiratory infections.

The experimental animals in Chodounsky's studies were chilled by exposure to ice-baths and cold draughts until their rectal temperature was lowered from 1° to 7° C. He employed several kinds of animals and several different pathogenic bacteria.

Virulent pneumococcus cultures by inhalation were used with one rabbit and one guinea-pig, with similar animals for controls. The rabbit was infected and died, but the guinea-pig as well as the two controls survived.

Intravenous injections of pneumococci were also employed with practically identical results in the chilled and control animals.

The Bacillus Friedländer in virulent cultures was used by intratracheal injections in dogs and by inhalation with Buchner's apparatus in guinea-pigs; 6 dogs and 2 guinea-pigs with a similar number of controls were employed. Of the dogs, 2 experimental and 3 controls were infected; of the guinea-pigs, one each of the experimental and controls.

Chodounsky also used cultures of Friedländer's bacillus attenuated by heat to determine if after chilling animals such cultures might infect them. Intratracheal injections in 4 experimental dogs and 4 controls failed to infect any. Later, one of the controls was injected with a virulent culture and promptly succumbed. Chodounsky also experimented with intravenous injections of pneumococcus in guinea-pigs, with intraperitoneal injections of Friedländer's bacillus in rats and with subcutaneous injections of diphtheria bacilli either alone or in combination with streptococcus, and in all of these found no difference in reaction between the chilled and control animals.

More interesting and perhaps even more instructive are the results of Chodounsky's self-experimentation. He describes himself as a man, aged fifty-seven years, subject to catarrh, frequent bronchitis, and lumbago. He reports in detail the results of 27 separate experiments upon the effect upon himself of severe exposure to cold. After hot baths, after ice-cold baths, and even when suffering from an acute coryza he exposed himself naked to cold air

and draughts at temperatures varying from 3° to 12° C. for periods of time varying from twenty minutes to one hour. Such exposure often caused very severe shaking chills, but no permanent effect of any kind and no symptoms of any of the pathological conditions usually ascribed to exposure to cold.

Recently, Kline and Winternitz[5] in the course of their studies of experimental pneumonia in rabbits, found that in animals which were exposed to cold, 4° C. after the ingestion of alcohol every day for periods varying from one to nine days, that 4 out of 7 rabbits died as a result, 2 of which showed intense laryngitis, tracheitis, and bronchitis, and 1 a bronchopneumonia. One other animal was killed at the end of three days and showed patchy congestion in the lungs. In the 2 remaining animals cultures of pneumococcus were injected intratracheally and death occurred in both, with lesions in lungs and upper air passages. Pneumonia rarely occurred after such injections to animals not exposed to the effects of cold and of alcohol.

The weight of the experimental evidence thus reported appears to be against Chodounsky's contention that exposure to cold has no influence upon respiratory disease, and with this evidence the results of our experiments are in accord.

The method of action of these secondary factors in infection is open to discussion. The lowering of general or specific resistance to infection may be considered. It has been shown by a number of observers, including ourselves,[6] that the production of such antibodies as hemolysins and agglutinins is affected by atmospheric temperature, especially, however, by heat.

On the other hand, changes in the local resistance of the mucous membranes of the upper air passages may be more important. That definite circulatory changes do occur in the upper air passages as a result of varying atmospheric temperature has been observed in animals and also in clinical experiments upon human subjects by one of us,[7] in collaboration with Cocks, which corroborated similar observations by Hill and Muecke.[8] In these experiments the results appeared to be due to the direct action of air upon the mucous membranes and not to a reflex from the surface of the body. The possible concern of vagus control in this action, as suggested by

Kline and Winternitz,[9] is worthy of serious consideration. The fact that infection of the normal respiratory tract is experimentally difficult, tends to emphasize the probable importance of the local changes in the mucous membranes favoring the entrance of bacteria, as the main predisposing factor in the problem under consideration.

Conclusions. 1. Respiratory infection of rabbits with Bacillus bovisepticus (snuffles) is favored by the chilling of such animals after they have been accustomed to heat.

2. The character of this disease, which occurs frequently in rabbits under natural conditions, makes the application of the experimental results to similar respiratory conditions in man less open to objection than in similar experiments with other infections.

3. The weight of experimental evidence, including our own, does not justify the elimination of exposure to cold as a possible though secondary factor in the incidence of acute respiratory disease.

4. From the limited data of our last two experiments it is suggested that any marked change of temperature predisposes rabbits to this infection, the severity of which varies with the amount of change, and that a change from low to high has an even more marked effect than that from a high to low temperature.

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DISCUSSION

Dr. Henry Sewall, Denver, said the work reminded him of experiments made by Baker at Ann Arbor nearly thirty years ago: monkeys were put in ice-water and then exposed to the breeze; then back into the water and exposed to the breeze again; but the animals thrived. They died in a few days, however, when they were confined in an old cellar room in which dead bodies for dissection had been kept.

Dr. S. J. Meltzer, New York, said it seems to him that experiments, as they are carried out at present, which seek to show the relations between exposure to cold and lung infection, must fail, because the lungs are always maintained at the same temperature. But the same cannot be said of the nose and larynx; exposure to cold does cause a reaction in these parts which leads to sneezing and coughing. These symptoms, however, are not parts of the disease; on the contrary, they are efforts on the part of the body to get rid of undesirable substances and may prevent the development of a disease. But while these effects of exposure do not cause directly diseases, they undoubtedly open the way to them.

The only way to test the matter so far as the lungs or bronchi are concerned would require the introduction of hot or cold air through a rubber tube into the lung or rather into the bronchial tree where organisms had been previously placed. But even this method may not bring forward complete evidence as to the influence of temperature.

ON THE VALUE OF RÖNTGEN-RAY EXAMINATIONS IN THE DIAGNOSIS OF CANCER OF THE STOMACH

By F. H. BAETJER, M.D.

AND

JULIUS FRIEDENWALD, M.D.

BALTIMORE, MD.

It is a well-known fact that the diagnosis of cancer of the stomach is often exceedingly difficult, and especially is this true in regard to the early recognition of this affection. Even although the morbid process may have assumed considerable proportions, many of the important manifestations may still be absent, so that even at a relatively advanced stage a correct diagnosis, based upon the symptomatology, is often impossible. Any new method, therefore, which promises substantial aid in solving this intricate problem must be regarded as a very welcome addition to the means we already possess.

The *x*-ray has presented us with an additional method of diagnosis in the study of gastric cancer, and although like other methods of medical diagnosis which are not absolute, it is probably more correct than any of the other means for diagnosis which are common at the present day. Its findings, however, should always be taken in conjunction with the clinical findings before the final diagnosis is made.

In the *x*-ray study of cancer of the stomach it is important, first of all, to recognize the varying positions and functions of the stomach under normal conditions.

The fundamental difficulty lies in the fact that the stomach is not a hard and fixed body; for we know that a perfectly normal

stomach may present great variability, not only as to position, but also as to motility and the expulsion of its contents. As a matter of classification we may divide the various types of stomach into three classes—first, the stomach of the fleshy individual; second, the stomach of the medium-weight individual; and third, the stomach of the thin individual.

The three classes of stomachs differ very materially as to shape and position.

In the first group we are dealing with a high stomach, the pylorus lying to the right of the median line, well up under the gall-bladder region, and occupying an almost horizontal position. In the second group we have the stomach of the medium-weight individual, which is generally cow-horn in shape, the pylorus resting in the median line, or just to the right of the spine. In the third group we are concerned with the stomach of the thin individual, which lies to the left of the median line, and is generally prolapsed and fish-hook in shape, with the fundus well down in the pelvis. Associated with these various conditions, we have corresponding differences in the motility of the stomach.

It can easily be seen that, in the first two types, not only the motility, but also gravity aids in emptying the stomach, whereas in the third class we have gravity acting against its normal motility, inasmuch as the pylorus and duodenum are always from two to three inches above the fundus of the stomach.

We have no hard-and-fast rule, therefore, according to which we can say that the stomach must empty itself in a certain number of hours, and that, if this time be prolonged, we are justified in concluding that we are dealing with some pathological condition.

In the first class the stomach empties itself in about three hours; in the third class it takes about six hours. Hence the question of any beginning obstructive lesion is dependent very largely on the character of the stomach with which we are dealing. Another difficulty to be encountered lies in the fact that the motility of a normal stomach may be affected by conditions outside of the organ itself.

Consequently, in dealing with carcinoma of the stomach we cannot rely on the size, shape and position of the stomach or upon

the retention of its contents. Our determination of the special lesion is dependent upon the study of two conditions, namely, the peristaltic waves of the stomach, and the many irregularities, or filling defects, in the organ itself. Unfortunately, as we have already noted, we possess no normal type of stomach from which we can draw comparisons; consequently, we are forced to determine the type of stomach that is normal for the individual undergoing the examination.

It is a well-known fact that the motility of the stomach is more or less affected by lesions in the organ itself, the degree to which it is affected varying according to the location of the lesion.

As a matter of classification we may divide the carcinomatous lesions of the stomach into three classes; first, lesions in the cardiac end of the stomach; second, lesions in the body of the stomach not affecting the orifices; third, lesions at the pyloric end of the stomach. In each of these conditions the activity of the stomach is materially affected, but in quite a different manner.

In lesions of the cardiac area of the stomach the cardiac orifice is almost always affected, and the patient comes for an examination because there is difficulty in deglutition. An examination reveals a stricture of the cardiac orifice together with a small or large filling defect in the immediate vicinity. The activity of the stomach itself is normal and, unless the lesion is very extensive, there is no interruption in the peristaltic waves.

In lesions in the body of the stomach one may have an extensive growth, and yet the patient may complain of very few symptoms, inasmuch as the motor activity is not interfered with. As this lesion rarely affects the cardiac or the pyloric orifice, obstructive symptoms are absent, the stomach emptying at the normal rate or perhaps a little more rapidly than normally. The Roentgen-ray examination of the stomach of this form generally shows that the peristaltic waves are interrupted in their course at the seat of the lesion, inasmuch as the lesion itself is hard and indurated, and does not admit of further peristaltic movements. In addition a persistent filling defect is almost always present. This filling defect is produced by the growth in the stomach wall bulging generally more or less into the lumen of the organ itself, so that it is outlined

by the bismuth in the stomach proper and presents the appearance of an indentation. In the third class of cases, that is, in lesions about the pylorus, the symptoms arise early as a rule and are due to a partial obstruction which quickly attracts the patient's attention to the gastric disorder.

From a roentgenological point of view we classify growths at the pylorus into two forms.

The first, the annular carcinoma, has its origin within the pylorus itself, and, although it may be very small in size, produces symptoms relatively early, as it soon causes a greater or less degree of obstruction.

The second type also has its origin at the pylorus; it is not annular in form, but invasive, most frequently extending along the wall of the stomach, especially at the pylorus. Such a growth may, or may not, produce early obstruction.

The annular type of carcinoma is easily recognized, inasmuch as the stomach is observed to be perfectly normal except at the pyloric end. The pylorus, instead of being clear-cut and sharp, is generally somewhat thickened and slightly depressed in the center, so that the structure assumes the shape of a crater.

The second type of carcinoma may exist for some time without being recognized, because in the absence of any symptoms of obstruction the patient, being still in a comfortable state, does not present himself for an examination. In this type of growth one finds a persistent filling defect in or close to the pylorus, and ascending away from it. The mass is indurated and free from peristaltic waves, since the waves pass over the area and are lost.

In cases of partial obstruction the stomach begins to show a very definite change. In the early stages we find active contractions of the organ with a slow elimination of its contents. Another very significant sign is that a portion of the stomach just within the pylorus and on the greater curvature in the pyloric region shows a tendency to bulge. The cause of this condition is as follows: The active contractions of the stomach force all of the food toward the pyloric region; the pylorus not being patent, as a result of this constant pressure the prepyloric region becomes dilated, so that the plate presents the pylorus, apparently not at

the end of the stomach, but with the prepyloric region extending farther to the right than the pylorus, the latter resting on top of the stomach, and pointing to the splenic region. This prepyloric bulging is dependent largely upon the duration of the affection. In the early stages it is very small, but, as the condition advances, it may reach the size of a hen's egg. As the condition advances still further, dilatation begins to take place, and after a time practically the entire fundus yields, so that a typical saccular formation is produced and all the bismuth rests in the fundus. When the stomach is in this condition, an *x*-ray examination will show a retention of contents for from 10 to 20 hours.

Unless due care be exercised, one may easily be misled by certain reflex or spastic conditions of the stomach. It is not uncommon to observe a stomach presenting a persistent filling defect in a definite area continuing over a period of an hour or two, and in a single instance under our observation for 48 hours, due to this condition. In doubtful cases the question of spasm of the stomach can easily be eliminated by the administration of full doses of atropin for one or two days, until the patient is well under its influence. A second examination, made under these conditions, will immediately show that the suspicious area has completely vanished, and that the condition previously observed was due to spasm.

In the *x*-ray study of gastric carcinoma the differential diagnosis between this condition and ulcer is often very difficult. It is still a much-debated question as to whether carcinoma of the stomach has its origin primarily as such, or is the result of a transition from an old ulcer. If the latter view be correct, one can readily understand the difficulty in determining when the benign condition begins the transition into malignancy. The situation of both carcinoma and ulcer is very frequently the same, although we observe carcinoma more frequently on the greater curvature than ulcer.

In the differential diagnosis between the two conditions the points to be taken into consideration are as follows:

1. Peristalsis. In carcinoma, unless there is obstruction, there is always hypermotility with rapid evacuation of contents. In

ulcer there is always hypermotility, with a spasm of the pylorus and more or less retention of contents.

2. Position. Carcinoma may occur in any part of the stomach. The invasive lesions are more frequently seen on the lesser curvature near the pylorus, and less frequently on the greater curvature. The massive growths are more generally seen on the greater curvature, whereas ulcer is generally observed on the lesser curvature near the pylorus, although it may occur on the greater curvature.

3. Filling Defect. In carcinoma the filling defect is generally surrounded by an invasive area, which, while not appearing on the plate, interferes with motility, producing an apparently large dead area. In ulcer the filling defect is much smaller, and is not so apt to have the immediate peristaltic waves interfered with, although, if the inflammatory area be large, there may be also a dead area surrounding the filling defect.

Carcinoma of the pylorus in the earliest stage is generally annular and produces a crater-like appearance. In ulcer of the pylorus there is a filling defect, but it does not generally assume the crater-like appearance.

When any of these conditions pass on to the obstructive stage, the change that is caused by the dilatation may mask the signs associated with the filling defect.

In our experience, in the very early stages of gastric cancer, it is frequently impossible to determine whether we are dealing with a malignant or a simple ulceration. Our main aim, however, is to decide whether the lesion at hand is really an ulcer, or not. Inasmuch as indurated gastric ulcers have at times a tendency to become malignant and produce roentgenograms similar to those which are cancerous, they must be included in the same class. The exact diagnosis must be cleared up by further investigation into the clinical history and the examination. But even under these conditions there are many instances in which the diagnosis may still remain in doubt until operation and microscopic examination of the specimen after removal finally establish the true nature of the disease.

In the later stages of gastric cancer, however, when the growth is large, it is usually a very simple matter to arrive at a correct

conclusion regarding its malignancy, but at this stage the symptoms are usually so well established that it is hardly necessary to seek further evidence by means of Roentgen-ray examinations.

The *x*-ray, however, even at this stage, furnishes us important evidence as to whether the tumor is or is not operable, inasmuch as it clearly establishes the location and extent of the growth, together with the degree of obstruction. Hence, in many instances, it will indicate the usefulness or uselessness of surgical procedures.

Since we have taken up the positive phase of gastric cancer, it is well to draw some conclusion regarding the negative findings. If the fact can be established that there is an absence of all morphological defects in the wall of the stomach that the peristalsis of this organ is normal, and that there is no tendency to even a partial obstruction, carcinoma of the stomach can usually be ruled out. This is an exceedingly important procedure, as a negative finding is of quite as much importance as a positive one.

In our Roentgen-ray study of gastric cancer we have selected 50 consecutive cases, including those only concerning which we could feel confident of the correctness of the diagnosis. Of these, the growth was located in 34 instances about the pylorus; in 9 it involved the body of the stomach without interfering with the orifices, and in 7 the cardia was involved. It is interesting to note the relative incidence of the other signs of the disease in these special cases at the time when the *x*-ray examinations were made.

Of the 50 cases, the gastric secretion was obtained in 46. There was a normal acidity in 4 instances; a hypochlorhydria or an absence of acid in 36 instances, and a hyperchlorhydria in 6 instances.

In the 36 cases showing a hypochlorhydria, lactic acid was present in 28 instances, and the Oppler-Boas bacillus in 24. Occult blood was present in the stools in 42 of all the cases.

A palpable tumor was observed in 34; dysphagia in 7; pain was present in 49; vomiting in 44; gastric hemorrhage in 14; melena in 8; occult blood in 46; dilatation of the stomach in 24 cases.

Of these cases the *x*-ray gave positive evidence of disease in

46 instances, of which 4 were early cases and 42 were late cases. In 2 of the 4 early cases the roentgenogram gave a positive diagnosis of carcinoma. In the other 2, however, an ulcerative lesion was found which was thought to be benign. The *x*-ray evidence, then, was positive in 42 of the late cases. It was positive, as far as the lesion was concerned, in all of the cases, but positive in only 95 per cent. of the cases as regards the actual diagnosis of carcinoma. In the early cases the *x*-ray showed a lesion in all; in 2 of them, however, it was thought to be benign, but exploration proved the condition malignant.

This method of examination, according to our experience, possesses about the same diagnostic value as any of the other early signs of this disease, when taken alone, but in conjunction with the clinical evidence a positive diagnosis can almost always be made.

Inasmuch as the *x*-ray clearly reveals the evidence of an indurated ulcer in most instances, and in view of the fact that indurated ulcers are at times the beginning of cancerous growths, it affords a means of establishing early the diagnosis of gastric cancer.

From our studies of the many cases of cancer of the stomach, in which *x*-ray examinations have been made, we believe that we are justified in drawing the following conclusions.

1. The Roentgen-ray offers most valuable assistance as an aid in the diagnosis of gastric carcinoma; and this is especially true when the lesion is situated in the so-called silent area. It should not be relied upon alone in the diagnosis of early cases without a strict consideration of the clinical aspect of the disease, but, when taken in conjunction with the other signs, it is of the greatest diagnostic value.

2. Indurated gastric ulcers give roentgenograms similar to those of carcinoma; but inasmuch as ulcers are frequently precursors of cancer, they may be grouped for practical purposes in the same class. It is often possible to determine their true nature only by microscopic examination of the excised area.

3. In the diagnosis of carcinoma of the stomach two conditions must be taken into consideration; first, the peristaltic waves of the stomach; and second, the morphological defect in the stomach.

4. In carcinoma of the cardiac area of the stomach there is usually a filling defect present, the activity of the stomach itself being normal, and, unless the lesion be very extensive, there is no interruption in the peristaltic waves. In lesions of the body of the stomach the peristaltic waves are interrupted in their course at the seat of the lesion, because the lesion itself is hard and indurated, and does not admit of further peristaltic movements. There is also present a persistent filling defect. In pyloric carcinoma there are usually signs of early obstruction in addition to a filling defect of small or large size, according to the extent of the growth.

5. In carcinoma, unless there be obstruction, there is always hypermotility with rapid evacuation of contents. In ulcer there is hypermotility with pylorospasm, and more or less retention of contents. In carcinoma the filling defect is generally surrounded by an invasive area, interfering with the motility, and producing a large dead area, whereas in ulcer the filling defect is much smaller, and is not so apt to interfere with the immediate peristaltic waves.

6. The Roentgen-ray furnishes us with important evidence regarding the operability or non-operability of the growth, pointing out, as it does, the location and extent of the growth, together with the degree of obstruction and the amount of involvement.

7. Negative findings are at times quite as important as positive ones, inasmuch as absence of the various *x*-ray signs of cancer affords presumptive evidence of the absence of this affection.

DISCUSSION

Dr. Julius Friedenwald, Baltimore, said that he does not regard the *x*-ray as an infallible guide to the diagnosis of gastric cancer; the *x*-ray findings must be considered along with all other diagnostic data.

Dr. Franklin W. White, Boston: Dr. Friedenwald has laid stress on the value of the *x*-ray in the diagnosis of early cancer. With this I do not altogether agree. The hope of early diagnosis of gastric cancer by this means, rests on the assumption that distinct anatomical changes precede symptoms. A recent study of a large series of cases has shown that this

assumption is not true, whether the disease be primary cancer or cancer secondary to ulcer.

The direct diagnosis of early gastric cancer has proved very disappointing. First, the patients, frequently, do not come early. Second, the *early* anatomical changes like the symptoms are hard to recognize. The earlier the lesion, the less clear the evidence, and attempts at *very early* diagnosis of gastric cancer are just as often wrong as right. There remains after examination a good-sized doubtful group.

The annular character of the *x*-ray defect has been hailed as a new sign of gastric cancer. It is more common in cancer but also found in ulcer. Indirectly the *x*-ray helps somewhat in the early diagnosis of cancer by discovering the location and size of ulcers of the stomach, thus showing which are more likely to become cancerous.

DISSOCIATION OF PARENCHYMATOUS (NEURONIC) AND INTERSTITIAL (NEUROGLIA) CHANGES IN THE BRAINS OF CERTAIN PSYCHOPATHIC SUBJECTS, ESPECIALLY IN DEMENTIA PRECOX*

By E. E. SOUTHARD, M.D.
BOSTON, MASS.

I BROUGHT before the Association in 1914 some considerations as to the analysis of cortical stigmata and focal lesions in certain psychoses.[1] I pointed out some promising paths of histopathological research in the cerebral cortex, illustrating my contentions from cases of a disease or diseases clinically known as dementia precox. We are indebted to the cortex topographers—among whom we may name Bolton, Campbell, Brodmann, of the moderns—for the rich lines of research which now open out to the neuropathologist. It has become the duty of the neuropathologist in this new phase of cortex histology to study comparatively the tissues of the "arrival platforms" (sensory), and those of the "departure platforms" (motor), and of the intermediary and more recently evolved tissues of the so-called "elaborative" or "psychic" nature.

Perhaps the best modern description of the new views is to be found in Bolton's recent work on *The Brain in Health and Disease*,[2] with many of whose general contentions most neuropathologists would agree.

* Contribution of the Massachusetts Commission on Mental Diseases, whole number 164 (1916.22). The previous contribution, 163 (1916.21), was by H. M. Adler, entitled "A Psychiatric Contribution to the Study of Delinquency," to appear in American Journal of Criminal Law and Criminology.

My own attention has been attracted by the technical advantages for differential histopathological analysis of cortical tissues of strikingly different architecture lying adjacent to one another. For example, the sensory arrival platform for vision, as represented by the calcarine type of occipital cortex, lies in close proximity to visual elaborative, or so-called "visuopsychic" tissue (to employ Bolton's term), namely, the common occipital type of cortex. These two tissues exist under virtually identical physicochemical conditions. I have found in certain cases a sharp histopathological differentiation in these tissues, which tissues not only exist antemortem under identical conditions, but may be passed through a variety of technical procedures postmortem of identical nature and terminating in material which can be comparatively examined under a single small cover-glass. One of the cases adduced in my former communication proved to show certain chronic changes in the elaborative or visuopsychic tissue, whereas the visual arrival platform or sensory tissue remained without obvious lesion. The case in question clinically showed pronounced and appropriate psychotic symptoms in the shape of certain sharply defined visual hallucinations; whereas the visual function in general was apparently quite normal. Such distinctive correlation between visual hallucinations and visuopsychic tissue lesion is almost (as one might say) too good to be true, and very possibly the hallucinations were really due to some functional involvement of these tissues quite apart from the obvious gliosis of the so-called visuopsychic tissue. The lesions, in fine, may merely be indicators of the true mechanism or chemism of the psychotic symptoms.

Turning attention in 1915 to the technical details of the task of the neuropathologist in the illustrations and interpretation of finer changes, I pointed out the advantages of a truly pathological classification of nerve cells.[3] It appeared that certain apparently homologous and at any rate analogous cell types had surprisingly different survival values. Thus, the large Betz cells, or so-called giant cells of the cerebral cortex, were found exceedingly resistant to certain types of tissue destruction, whereas those very kinds of destructive processes made short work of the large Purkinje cells, or giant cells of the cerebellar cortex. I am bound to say that further

work may show that under some conditions the large cells of the cerebrum and of the cerebellum may live and die, as it were, together, and evince identical survival values under said conditions. With the material at hand, however, I felt sufficiently satisfied to propose a comparative study of the differential viability of the various nerve cell types.

I seemed to see as a construction of the future an essentially "pathological" classification of nerve cells on the basis of their powers of resistance or survival values. I thought that the neuropathologist might well proceed to collect data as to the differential effects of simplification or decomplication of nerve tissues. Are there not, however, cases always outstanding in which there are no such changes; psychoses in which, namely, the brain and especially the cerebral cortex is acting abnormally but shows no structural sign of its abnormal action? Are there not, in short, cases in which the brain is theoretically and intrinsically entirely normal and merely acting abnormally under the stress of conditions exogenous to the nervous system? This is the problem of normal-looking brains in the psychoses, contributions to which have been made by several workers in Massachusetts institutions for some three or more years past.[4-8]

Are there cases in which, however carefully we shall study the elaborative tissues alongside the arrival and departure platforms, we shall not find lesions of importance? Are there cases in which the problem of the survival values of different types of nerve cells will not be at all in play? Is there anything in the neuropathological literature or elsewhere which goes definitely to prove that the clinical phase of a psychosis is identical with a phase of cell injury? Is it certain that the period when a patient shall seem mentally altered to a skilled observer is identical with a period in which coarse or fine anatomical methods shall demonstrate important structural lesions? Is there not, in short, a group of cases in which the solution of the psychotic problem is entirely removed from the zone of cortex histology, and even theoretically of cortex chemistry and physics, simply because the cortex is presumed to be working under quasi normal conditions? Is there not a problem of the psychoses which we may term the problem of "discords

played on good instruments?" Unless some answer to this question can be given, the theory of the genesis of the psychoses is likely to be at loose ends.

Accordingly I felt it of strategic value in this work to study a group of normal-looking brains, to isolate if I could a number of convincing examples of *psychoses of definite and relatively permanent nature, in which cases pertinent lesions should be absent or negligible.* I had forthwith to disregard great numbers of brains with a number of lesions, not because I was entirely sure that these lesions were correlated with the psychoses, but because they clouded the issue of determining absolute normality for the brains. Even on the standards of the autopsy table, something like two-thirds of the brains that accrue from a hospital of committed types of mental disease exhibit more or less pronounced gross lesions, largely of an atrophic nature or of such a nature that the differential diagnosis between acquired atrophy and inborn hypoplasia cannot be made. If the neuropathologists at work are a bit structuralistic, then, as in our Danvers material, about three-fourths of the brains turn out to be abnormal in some important way. The finer structural diagnosis yields in this event still more cases of an atrophic or hypoplastic nature, and tends to exhibit a remarkable preponderance of such conditions in the frontal lobes. In fact, the frontal lobes in the hands of some observers are found atrophic or hypoplastic in greater or less degree in two-thirds of relatively long series of brains.

In several years' work I developed certain criteria of the normality of the brain which may be in part within the personal equation, but which, applied to a Boston State Hospital series (in the hands of my colleague, Dr. M. M. Canavan), left only one-eighth of all the brains of a series of 145 subjects without gross lesions of apparent significance, or of such a nature that it would be dangerous to say that the lesions were without relation to the psychoses. Whether cystic, atrophic, hypoplastic, or otherwise characterized, the lesions in seven-eighths of the Boston series were too perturbing to deal with in the problem of "discords played on a good instrument."

Nineteen of the 145 brains studied at the Boston State Hospital in the years 1910 to 1913 by Dr. M. M. Canavan and the writer

turned out to be of a normal appearance in the gross (11.7 per cent.). These 19 cases were especially studied as to their clinical histories. Their previous histories and hereditary features were particularly looked into by a trained worker in eugenics (namely, Miss Anna E. Steffen) who went into the field after new data to correlate with the cases viewed in their entirety. Moreover, all the brains systematically photographed by Mr. Herbert W. Taylor under the supervision of Dr. Annie E. Taft, both before and after the removal of the pia mater, so that the upper, lower, lateral, and mesial aspects of each brain could be readily compared side by side.

Orienting microscopic examination was then made of a few areas in each of the 19 cases. One of the cases, for example, turned out to be microscopically a case of general paresis; another was very probably a case of the so-called central neuritis, with a variety of additional microscopic changes. Still another case showed striking universalized cell changes, also of an acute nature. Other cases showed convincing degrees of diffuse cell loss or of diffuse arteriosclerotic change of such a nature that one could hardly understand the alleged normality of the brains as observed at the autopsy table. A few of the cases were of brief duration and clinically of such a nature that it might be doubted whether they would upon survival have turned into cases of chronic mental disease. The clinical histories of some cases indicated such brief illness that it might well be doubted whether the brains would register gross atrophic changes in the time available.

However, in the course of the successive application of higher and higher powers (as it were) of logical analysis, we arrived at a set of 5 cases, which cases were all clinically of a sufficient duration to warrant the idea of relatively permanent mental change, had all been observed with adequate accuracy, could be fitted sufficiently well into prevalent classifications of mental disease, and *still failed to show, either at the autopsy or in the systematic photographic analysis of the cortical appearances, or even in the orienting microscopic examination of a number of areas, any convincing evidence of brain disease.* It is not that the microscopic examination failed to show changes, and possibly changes of some importance (as will be mentioned below); but the microscopic changes found in the orienting analysis

of these 5 brains were, after all, hardly striking enough to warrant correlation with the symptoms observed or the entities determined.

It seemed that these 5 cases, the product of successively more intensive analysis of a large series, might permit us to draw the lines a bit closer about the classical position of the psychiatrists as to generally functional psychoses. In any event, the classical position of various psychiatrists as to the functional psychoses is often based upon the vaguest of formulæ, perhaps even in some cases on the private ontological wish of some one that mechanistic or vitalistic views of mental disease shall prevail. It is clearly our duty in this situation to discover what the facts are about the very existence of these genuinely functional psychoses, the psychoses that proceed with utter intrinsic normality of the brains which are running along just as a physiologist might wish them to run.

I am far from holding that the observation of numerous minor lesions in a variety of loci in all of the brains in question proves that no brain in a psychopathic subject is structurally normal. No one could be so naïve as to suppose that association or correlation of lesions and symptoms amounts to a causal nexus between the lesions and symptoms. Still, I am bound to say that the functionalist wishing to prove that mental disease is consistent with a structurally normal cortex must find himself greatly at a loss when confronting the present material. Even with all due allowance for the personal equation in histological analysis (and only histologists are aware how wide is this margin), the changes found, varying as they do from brain to brain and from locus to locus within a given brain, must certainly be given due consideration. I conceive that no brains of normal non-psychotic subjects have so far been examined with equal thoroughness.

Without insisting upon gaining a decision in the struggle over intrinsically normal brains in the psychoses, and conceding the necessity of more material than here presented, I wish to offer some interesting considerations that came rather as a by-product of this work. These considerations I had intended to indicate in the title of this communication. The dissociation of parenchymatous and interstitial lesions, set forth in my title, will remind the pathologist of the older contentions concerning diseases, *e. g.*, of

the kidney. Such, for example, is Senator's classification of chronic forms of kidney disease. In point of fact, the cases of brain disease here studied do rather clearly show a tendency to pure parenchymatous disease on the one hand, to pure interstitial disease on the other hand, and to a mixture, or "diffuse" condition in one case. Of course, when it comes to kidney disease, the pathologist has often felt it a merely pious wish that chronic Bright's disease shall fall at all easily into parenchymatous and interstitial forms. Nor do I feel that the cerebral cortex or congeries of organs, still more labile than the kidney, is likely to permit a similar classification to click easily into place.

We must clearly consider that the scar stage of cortex diseases will complicate any picture. Equally when Volhard and Fahr, in their well-known monograph on Bright's disease, attempt to separate the nephroses from the nephritides, they are compelled to find scar stages in both types.[9]

The peculiar advantage for our present purpose of these 5 cases is that our study has proved them to be not yet in a scar stage, if indeed they were ever destined to become visibly and tangibly atrophic. Here are cases which have proceeded for a number of years without evidence of naked-eye change and without palpable changes to the finger. Microscopically, however, they prove to be in some instances the polar extremes of one another; a case with highly marked degenerative cell changes proves to show entirely negligible neurogliar changes. Another case with extremely marked neurogliar changes (though without induration in the gross) proves to have little or no parenchymatous change in the shape of cell degeneration.

Let us look more in detail at these changes. The following is a list of cases having brains normal looking in the gross, both as observed upon the autopsy table and after photographic analysis, and yet microscopically normal or with negligible or minor changes in eight orienting areas of the cerebral cortex.

Case.	Sex.	Age.	Onset.	Duration.	Diagnosis.
11.36 . . .	F.	31	29	20 months	Manic-depressive.
12.47 . . .	F.	27	25	2 years	Dementia precox.
13.7 . . .	F.	64	20	3½ years	Manic-depressive.
12.41 . . .	F.	60	50	10 years	Paranoia.
10.9 . . .	F.	56	42	14 years	Dementia precox.

The microscopic examinations were, although extensive, limited to observations of material prepared in two classical ways, namely, by a monochromatic nuclear stain demonstrating cell nuclei and cell bodies with sufficient clearness, and by the Weigert myelin sheath method. Notes were made of appearances in the following areas on each side: prefrontal, superior frontal, precentral, postcentral (taken superiorly), postcentral (taken inferiorly), superior parietal, angular, Broca, transverse temporal, superior temporal, middle temporal, insular, gyrus rectus, pyriformis, calcarine, making 16 areas on each side, or 32 areas in all. Owing to technical difficulties, occasional areas could not be completely studied and were omitted.

Notes were made as to the appearances, as a rule, in seven zones of the cortex and in the underlying white matter. The resulting tabulations included 144 to 232 histological observations upon nerve cells, neuroglia cells, satellite cells, axonal reactions, chromatolysis, pigmentation, arterial changes, etc., in separate loci defined by area and layer. An endeavor was made to include among nerve cell changes, besides axonal reaction and pigmentation, also the somewhat more difficult diagnostic points of cell swelling, cell shrinkage, diffuse staining, deep staining, pale staining, and the like, some of which changes are, of course, difficult of interpretation, and are even within the range of the personal equation.

The following table shows the proportion of lesions noted in the loci observed in these 5 cases.

Case.	Diagnosis.	Duration.	Loci examined.	Lesions noted.	Ratio of lesions to foci.
11.36	Manic-depressive	20 months	152	111	73
12.47	Dementia precox	2 years	232	193	83
13.7	Manic-depressive	$3\frac{1}{2}$ years	144	121	84
12.41	Paranoia	10 years	208	149	71
10.9	Dementia precox	14 years	224	122	54

It is clear that these so-called *lesions* are of various nature and of very varying significance to the psychoses in question. Accordingly a collation of the lesions noted has been made to show the proportion of what we regard as nerve-cell losses and of what we regard as proliferative changes. We freely grant the difficulty of a diagnosis

of nerve-cell losses upon qualitative grounds and without adequate measurement and possible photography. However, we present our analysis for what it is worth:

Case.	Diagnosis.	Duration.	Loci observed.	Nerve-cell losses diagnosticated.	Ratio of supposed nerve cell losses.	Evidences of neuroglial proliferation observed.	Ratio of proliferative changes.
11.36	Manic-depressive	20 months	152	66	43	12	7
12.47	Dementia precox	2 years	232	123	53	7	3
13.7	Manic-depressive	3½ years	144	33	22	55	38
12.41	Paranoia	10 years	208	91	43	24	11
10.9	Dementia precox	14 years	224	25	11	19	8

With all due concession of the difficulty of making a qualitative estimate of nerve-cell loss, it is entirely clear that these cases tremendously differ among themselves in the matter of nerve-cell loss as we render the diagnosis. Compare for example the 11 per cent. of nerve-cell losses in Case 10.9 with the 53 per cent. of loss noted in the various loci of Case 12.47. Almost any histopathologist would readilly agree that it is far easier to make a diagnosis of neuroglia proliferative changes than of nerve-cell losses on account of the fact that in cellular gliosis we deal with positive added factors in the shape of clearly observable nucleated cells. It is clear from the great disparity in percentages of proliferation as compared to cell fosses either that gliosis does not run *pari passu* with nerve-cell losses or that our diagnosis of nerve-cell losses errs in the direction of finding too many losses. However, just as in the case of the nerve-cell losses, so also in the case of the neurogliar proliferative changes, we find a great range of differences; thus in Case 12.47, we find but 3 per cent. of proliferative changes whereas in Case 13.7 we find 38 per cent. Without closer analysis, it is clear that Case 12.47, having the highest percentage of nerve-cell losses (53), is precisely the case which has the lowest percentage of proliferative neurogliar changes (3). It is clear that Case 11.36 and Case 12.41 tend in the same direction since Case 11.36 shows 43 per cent.

cell losses to 7 per cent. neurogliar proliferative changes and 12.41 shows 43 per cent. of nerve-cell losses but 11 per cent. of neurogliar changes. On the other hand, Case 13.7 shows the opposite tendency, for it contains the highest percentage of neurogliar proliferative changes, namely, 38 and next to the lowest percentage of nerve-cell losses, namely, 22. Conditions in these two directions of nerve-cell loss and neurogliar proliferation are numerically about even in the fifth case, namely, 10.9.

A number of tentative conclusions might be drawn from these cases but it is worth while to analyze the findings more in detail and to examine the clinical histories before rendering these conclusions. First, let us present in tabular form some details of the microscopic findings in these cases. The columns deal with the white matter, the undermost or fusiform layer of the cortex and then in succession the layers of internal large pyramids, stellate cells, external large pyramids, medium pyramids, small pyramids and the plexiform layer. The findings in regions like the occipital which do not entirely agree in general construction and nomenclature with the other areas of the cortex have had their findings listed under the headings of those areas which are most nearly homologous with the areas just listed.

The abbreviations in the columns are as follows:

axre	= axonal reaction.
artscl	= arteriosclerosis.
cegl	= cellular gliosis.
chrly	= chromatolysis.
irreg	= irregular grouping of cells.
l	= loss.
perigli	= perivascular gliosis.
perivdep	= perivascular cell deposit.
pig	= pigmentation.
sacpig	= saccular pigmentation.
satc	= satellite cells.
shr	= cell shrinkage.
sm	= small cells.
vth	= vessels thick.

I hope to publish elsewhere the details of the clinical, anatomical, and histological examinations of these 5 cases, but for the present purpose I will mention only a few of those features which seem particularly pertinent to the question of the dissociation of parenchymatous and interstitial lesions.

	White matter.	Fusiform.	Internal large pyramid.	Stellate.	External large pyramid.	Medium pyramid.	Small pyramid.	Plexiform.
11.36 Manic-depressive 20 months	3 perivdep 1 perivgli 5 vth	1 axre 2 satc 10 l 1 irreg	3 axre 1 chrly 1 satc 1 shr 12 l	1 satc 1 shr 10 l 3 irreg ..	4 axre 2 satc 1 shr 10 l ..	1 axre 2 cegl 1 satc 1 pig 1 shr 13 l	2 cegl 11 l 3 shr 1 vth 1 irreg	0
	9	14	18	15	17	20	18	0 = 111
12.47 Dementia precox 2 years	12 artscl 1 l 1 vth	13 axre 1 satc 15 l 1 sacpig	3 axre 2 chrly 1 sacpig 1 irreg 3 shr 2 satc 17 l	4 axre 1 shr 23 l	5 axre 1 chrly 4 shr 18 l 1 sm	1 axre 1 irreg 4 shr 24 l 1 sm	1 cegl 25 l 2 shr 1 sm	3 cegl
	14	30	29	28	29	31	29	3 = 193
13.7 Manic-depressive 3¼ years	3 pig 1 perigli 1 cegl 6 vth	5 satc 3 shr 2 pig 7 l 3 cegl	4 satc 2 axre 6 pig 5 l 1 shr	2 satc 1 cegl	1 axre 8 satc 5 pig 2 cegl ..	11 l 3 satc 5 cegl 2 shr 1 irreg	10 c 4 cegl	17 cegl
	11	20	18	3	16	22	14	17 = 121
12.41 Paranoia 10 years	2 perivdep 8 artscl 1 pig 2 l	1 axre 1 cegl 8 satc 3 shr 2 sm 16 l	6 axre 3 shr 1 sm 14 l<..	3 axre 3 satc 15 l	1 sm 2 shr 14 l 2 axre 3 satc	4 axre 1 satc 1 shr 15 l	4 cegl 3 shr 15 l 1 satc	3 cegl 1 vth
	13	31	24	21	22	21	23	4 = 159
10.9 Dementia precox 2 years	6 pig 9 vth 3 perivgli	5 axre 9 satc 2 shr 2 irreg 3 pig 2 l	4 axre 3 pig 10 l 1 irreg 3 shr	4 axre 2 satc 1 vth 3 irreg 3 l	7 shr 3 satc 4 irreg 3 l 2 pig	4 axre 1 pig 4 satc 2 irreg 3 l	5 axre 1 irreg 1 shr 4 l 1 vth	1 vth 1 pig
	18	23	21	13	19	14	12	2 = 122

Let us consider, first, Case 12.47, that case in which the parenchymatous change was maximal and gliosis minimal. The cell lesions in this case were observed in 53 per cent. of all loci examined. Gliosis appeared in but 3 per cent. of all loci examined; that is, 123 examples of cell loss were noted in 232 loci; whereas but 7 instances of neurogliar proliferation were observed in these same loci. This case was one of dementia precox and was the youngest of these cases: an Irish servant girl, with some drunkenness and tuberculosis in the family, herself a victim of tuberculosis, and in point of fact developing symptoms after discharge from a sanatorium for tuberculosis; a case with two years of mental symptoms, dying

at the age of twenty-seven years. The autopsy showed sclerosis of the aorta and of the splenic artery; the heart muscle showed brown pigmentation, and the vascular vessels were small. Even the brain was not destitute of minor arteriosclerotic changes, more marked than in any other case of this particular series of 5. A bird's-eye view of the lesions would, in point of fact, suggest a greater age than the patient actually had reached. At first, apprehensive, depressed, slightly slow in reactions, the patient after some weeks became apathetic and unwilling to take food, became mute or whimpering, and finally completely non-coöperative, sitting for long periods in a particular attitude, and showing a characteristic and marked flexibilitas cerea. From this condition she fell into a sort of catatonic stupor, from which she emerged some weeks later in a euphoric state, able to feed herself and with a good appetite, but with loss of memory for recent and remote events and disorientation. Some months later, after headaches and dizziness and a fainting spell, the patient took to bed in what seemed to be a catatonic stupor, from which, however, she once rose and moved about.

If there is such a disease as dementia precox, it is probable that this case must be counted therein. Two years is probably a safe period in which to allow the development of atrophy, or at all events of a certain induration of the brain, provided that there were any tendency on the part of the tissues to gliosis. In but 7 loci out of the 232 examined was there any evidence of gliosis, and these evidences were for the most part examples of cellular gliosis in the outmost layers—a locus of election for such changes in a variety of diseases. Are we not here dealing with a comparatively pure example of mild but exceedingly wide-spread parenchymatous changes without tendency to neurogliar reaction? It is, of course, hard to believe that this case, had it lasted twenty instead of two years after onset, would fail to have shown far more gliosis. Just as the so-called nephrosis of Volhard and Fahr may pass into a scar stage of a secondary nature, so we may suppose that the brain tissues of Case 12.47—a case with maximal evidence of cell loss—might well pass into a stage of corresponding interstitial loss. I pass over comments concerning the correlation of particular symptoms with the distribution of lesions in particular loci, as without the scope of this paper.

Let us now throw into contrast with Case 12.47 that case (13.7) which showed the maximum degree of neurogliar change (38 per cent. of loci examined) and far less evidence of cell loss (22 per cent. of loci examined). This is a case, aged sixty-four years at death, diagnosticated manic depressive psychosis of a total duration of three and a half years, occurring in two attacks: one, an attack of so-called slight melancholia, a year in duration, beginning at twenty years of age; and the other before her death. The family, in this case, showed a number of instances of cardiovascular disease, and the abdominal aorta of the patient herself was found altered into a calcareous tube, with ulcers, vegetations, and a thrombus. In the head, the patient showed basilar arteriosclerosis; but the brain tissues so far as examined showed little or no evidence of fine arterial changes. In fact, the high percentage of gliosis cannot be related to vascular change with any probability. The gliosis is pretty generally distributed throughout the loci; many instances of cellular gliosis are found in the outermost layers, but satellitosis is especially marked in the inner layers, associated with more or less cellular gliosis. It is easy to claim that the gliosis is a phenomenon of age, and such it may actually be. The ordinary hypothesis for its production would be the loss of cells with the endeavor on the part of the neurogliar tissue to replace these cells. Bearing in mind that the brain was of normal appearance and weight (was, in fact, something like 200 grams overweight in relation to the body length: 1370 grams), we are confronted by the fact that the evidence of cell loss in the cortex is slight. If we are to suppose that the long lucid interval of decades between the attack in the twenties and the patient's death in the sixties ran on without special evidence of cell loss, and regard the mental disease as in nowise due to structural cell changes, then, perhaps, we may think of a progressive, slight but wide-spread, gliosis going on without special relation to the symptoms of the case. If we omit reference to the gliosis altogether, and compare this case (13.7) with the above-mentioned case (12.47), we perceive that a patient, aged sixty-four years, with three years and a half of symptoms, two years and a half immediately preceding death, exhibits but 22 per cent. of cell losses in loci examination as compared with 53 per cent. in a patient dying at twenty-seven

years after two years of symptoms. On the basis of parenchymatous change alone, accordingly, this oldish case of manic-depressive psychosis (13.7) is better off in nerve-cell content than a far younger case of dementia precox. Yet in both instances the play of lesions in the parenchyma has gone on without a proportionate amount of neurogliar change. The severely affected parenchymatous case (12.47) has little or no gliosis, and the far less severely affected parenchyma of Case 13.7 is supplied with a gliosis which we may possibly attribute in part to the mysterious operations of senescence.

A third case (11.36) is another case of comparatively brief duration, some twenty months or two years, with death at thirty-one. This case should be worth comparing with 12.47, having two years of symptoms with death at twenty-seven. This case shows somewhat less parenchymatous change: 43 per cent. in the loci examined, and somewhat more neurogliar change: 7 per cent. of loci examined. The first fact which attracts us in this case is the diagnosis: manic-depressive psychosis. This diagnosis was grounded upon the obvious mania of the patient on admission. Nevertheless, the patient herself described auditory hallucinations—a symptom of somewhat ominous character, and not often found in clearly defined form in good examples of manic-depressive psychosis. Again, the patient executed a variety of impulsive acts and showed stolidity and indifference in certain phases, together with persistent slight silliness, which may well be regarded as consistent with the diagnosis of dementia precox. The fact that the patient also showed symptoms characteristic of manic-depressive psychosis is not at all inconsistent with the theory of these diseases, since virtually every symptom of manic-depressive psychosis is nothing but an exaggerated or lessened degree of a normal phenomenon. Hence, as we currently say, dementia precox patients as well as all other mental patients may show manic-depressive symptoms; whereas the true manic-depressive patient fails to show anything but normal phenomena in abnormal degree. It would be hardly convincing to alter the diagnosis of manic-depressive psychosis to dementia precox in the light of cortex histology in the present dubious phase of this topic. I am inclined to feel, however, on the clinical data alone, that the case is one of dementia precox and that we would best

align Case 11.36 with Case 12.47 as cases developing a variety of dementia precox symptoms in the twenties and both succumbing to tuberculosis. Both showed cardiovascular tendencies; both were servant maids; both had a certain family taint: drunkenness and tuberculosis in one; neurosis, heart disease, diabetes, and tuberculosis in the other. Of course we may give ourselves leave to inquire whether the tuberculosis in these cases has a genetic relation to the mental disease or possibly to the parenchymatous changes in the brain. At all events there is something peculiar and interesting in these cell losses which are not accompanied by gliosis.

Another case (12.41) has as high a proportion (43 per cent.) of parenchymatous changes as did Case 11.36, although it possesses a slightly higher ratio of neurogliar changes (11 per cent.). Here is a case with symptoms of ten years' duration, with death at the age of sixty years. If it was easy to ascribe to old age the 38 per cent. neurogliar changes in Case 13.7, a woman dying at sixty-four years, it is remarkable that senescence has produced few neurogliar changes in Case 12.41. Moreover, in Case 12.41, a great many of the neurogliar changes are of the nature of satellitosis, changes, namely, which are rather more related with cell loss than with any senescent tendency to a general induration of the tissues. The diagnosis in this case is not too easy, although a delusional condition was paramount and the diagnosis paranoia or paraphrenia (in the newer Kraepelinian sense of this term) may be regarded as safe. The patient's father was dissolute and she early had illegitimate children, but thereafter her progress was upward, and upon refusal of her paramour to marry her, she left him and became active in church work, and in the course of years began to present an appearance of refinement. In the fifties, however, she became mildly deluded about her pastor, circulating stories of misconduct and talking of his influence upon her. After threats on his life, she was committed. She held the belief that the pastor had hypnotized her and had caused many deaths in his church.

This case, like Case 12.47 and 11.36, was also extensively tuberculous, having developed tuberculosis late in life.

Here, then, are three cases: Case 12.47, Case 11.36, and Case 12.41, aged at death twenty-seven, thirty-one, and sixty years

respectively, with tendency to marked parenchymatous change associated with but slight neurogliar changes, all three belonging very possibly to the group of endogenous deteriorations in the sense of Kraepelin; the first undoubtedly a victim of dementia precox, the second very probably so, and the third an early sex delinquent, later hyperreligious, becoming paraphrenic or paranoiac. When contrasting these three cases with a case pretty certainly not one of the so-called endogenous deteriorations, namely, Case 13.7, a case which showed two phases of manic-depressive psychosis, we have thrown into strong contrast the parenchymatous changes of our three "endogenous" cases and the lesser development of cell losses in the manic-depressive psychosis.

There remains for consideration one case—the most nearly normal case of our whole series—a case dying at fifty-six years of age, after fourteen years of frank symptoms, which received the diagnosis of dementia precox. This patient was of noble French extraction, and had a high-school education. She gradually developed from an apparently genuine jealousy a wealth of paranoid ideas about her family and acquaintances. She was given to extravagant accounts of her delusions, and went at times out of the hospital ward dressed in brilliant colors, youthfully, and with ribbons in her hair, and wore a lace coat of peculiar pattern. She was for years a striking patient, decorating herself with buttons, arranging her hair in small curls, and talking continuously and fantastically. She later developed auditory hallucinations and a number of hypochondriacal ideas. The cell losses in this case came to but 11 per cent., and the gliosis to but 8 per cent. Accordingly, if our method of judging lesions is correct, this case is the most nearly normal case in the series. There are some interesting points which may be published later concerning the distribution of lesions in different loci in these cases. From the present point of view, I wish to call attention merely to the distinction of this case from the other cases which we should perhaps term also cases of endogenous deterioration. I may call attention to the absence of active tuberculosis from this case.

Thus, in our whole series, the youngest patient (Case 12.47) showed the most instances of cell loss and the least instances of

neurogliar proliferation. On the other hand, the greatest number of instances of neurogliar proliferation occurred in the oldest patient (Case 13.7). Age alone, however, can scarcely account for the gliosis in Case 13.7, since another patient almost as old (Case 12.41) showed very little gliosis. The neurogliar changes are very possibly dissociated from the parenchymal changes.

If we turn from neurogliar changes to nerve-cell changes, we find that a case of manic-depressive psychosis (Case 13.7), although sixty-four years of age and the victim of a variety of somatic diseases, showed far less cell loss than 3 cases (Cases 12.47, 11.36, and 12.41) apparently belonging to the group of so-called endogenous deteriorations. We might at first sight suppose that the cases of endogenous deterioration are more prone to parenchymatous changes than to neurogliar changes. This may well be the case, but we must remember that these 3 cases also happen to be victims of severe tuberculosis. Moreover, we have another case (Case 10.9) and that the case of longest duration in the whole series (fourteen years), which not only showed a low percentage of neurogliar changes but a low, and in fact, the lowest percentage of parenchymatous changes. This most nearly normal case in our series was not actively tuberculous. It was most probably a case of endogenous deterioration. The changes in this case were singularly localized in certain regions, so that if the process exhibited in some loci were spread over the entire nervous system, the case would undoubtedly resemble the others of the endogenous series.

I cannot enter here the unsolved question of the relation of tuberculosis to dementia precox and the possibility of lytic changes somehow incidental to tuberculosis taking place in the nervous system. I am limiting the argument to the question of the dissociation of parenchymatous and interstitial changes.

We have thus considered:

1. The case with most instances of cell loss (Case 12.47).
2. The case with least instances of cell loss (Case 10.9).
3. The case with the most instances of gliosis (Case 13.7).
4. The case with the least instances of gliosis (Case 12.47).

And we have learned that there may be a marked lack of correlation between cell loss and glia proliferation (see especially Case 12.47).

The two remaining cases (Cases 11.36 and 12.41) resemble each other in both proportions (43 per cent. to 7 per cent., and 43 per cent. to 11 per cent.).

Three of the cases with large degrees of cell loss had no corresponding gliosis. These were cases probably belonging in the dementia precox group. They were all three very actively tuberculous.

The most nearly normal case of all was one that may perhaps be called paranoia. There was no active tuberculosis in this case. The lesions were exceedingly focal, though of the same general appearance (cell losses in a variety of loci) as those of the more wide-spread parenchymatous lesions.

To sum up:

1. Parenchymatous (neuronic) lesions and interstitial (neuroglia) lesions may be dissociated and combined, much as similar lesions in the kidney.

2. A case of manic-depressive psychosis failed to show convincing degrees of parenchymatous lesions.

3. Dementia precox cases had marked parenchymatous disorder, to which gliosis was not at all proportionate.

4. It is necessary to find and study by like methods a good group of non-tuberculous cases of dementia precox, so as to exclude tuberculosis from having a share in the production of these lesions.

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THE TOXIC EFFECTS OF UREA ON NORMAL INDIVIDUALS

By A. W. HEWLETT, M.D., Q. O. GILBERT, M.D.
AND
A. D. WICKETT, M.D.
ANN ARBOR, MICHIGAN

In order to throw light upon the nature of uremia, many investigators have studied the physiological effects produced when urea is administered to or injected into animals. The majority of those who have undertaken such studies were unable to demonstrate that urea acted as a poison. Only a few have succeeded in producing definite toxic effects. For example, Herter and Wakeman[1] as well as Marshall and Davis[2] found that approximately 1 per cent. of the body weight must be injected into animals in order to produce a fatal result. Ascoli,[3] in reviewing the earlier literature, has sought to explain the occasional toxic effects observed on one or more of the following assumptions: (*a*) The urea used was not pure, (*b*) it was injected intravenously in too concentrated a solution, or (*c*) where used in dilute solution the effects were attributable to the excessive amounts of liquid rapidly introduced into the body. Under any circumstances it is clear that in animal experiments definite toxic effects can be produced only when extraordinarily large doses of the drug were given, doses which presumably raise the concentration of urea in the body above that which is encountered in most cases of uremia in man. For these reasons the view has become generally accepted that the toxic effects of urea in any concentration encountered in patients are negligible and that the symptoms of uremia are due to the action of other and more poisonous substances.

Recent advances in our knowledge concerning the toxic symptoms presented by patients in the more advanced stages of nephritis

permit one, however, to approach this question from a new point of view. It seems established that uremia, in the sense of any toxic state complicating renal disease, includes a variety of distinct conditions. In certain patients toxic symptoms occur when the urea and the total incoagulable nitrogen of the blood are either not increased or are increased to such a small extent that the symptoms observed can hardly be attributed either to the urea or to an increase in the total incoagulable nitrogen of the blood. This appears to be particularly true of those cases of uremia in which generalized epileptiform convulsions dominate the symptomatology. In such cases particularly, the search for a specific toxic substance seems indicated and N. B. Foster[4] has reported the isolation of a toxic base from the blood of patients suffering from the convulsive form of uremia.

On the other hand, it has been shown that during the later stages of nephritis there is not infrequently an increase of urea and of other nitrogenous substances, such as uric acid, creatin, creatinin, and indican, in the blood and that when this increase becomes very marked toxic symptoms are present. In such patients the urea not only shows the greatest absolute increase but its increase is relatively greater than the increase in the sum total of the other non-protein nitrogenous bodies. Clinical studies have demonstrated, furthermore, that such patients frequently do not present certain of the classical uremic symptoms. Generalized convulsions, paralysis, and prolonged comas are often absent. The symptoms which characterize the advanced stages of nitrogenous retention have been the subject of study particularly by the French school of medicine for some years. According to Widal,[5] for example, the symptoms consist of loss of appetite, fatigue, prostration, mental dulness, somnolence and eventually coma. Reiss,[6] who has recently described this condition as the asthenic type of uremia, believes that it is characterized clinically by drowsiness and indifference, by bodily fatigue and prostration, and by sudden cardiac death without prolonged coma.

The modern blood studies on nephritic patients have also served to define the relation that exists between the clinical symptoms and the level of urea and non-protein nitrogen in the blood. While it is difficult, by reason of individual variations, to fix accurately the

level at which the retention of nitrogenous waste products leads to the production of symptoms, nevertheless one may say in general that symptoms characteristic of asthenic uremia are rarely well defined when the concentration of urea in the blood is less than 100 mgms. per 100 c.c. of blood and that they are rarely absent when the concentration exceeds 200 mgms. From clinical observations, therefore, one would be inclined to place the point at which the accumulation of urea might possibly cause symptoms between the two limits of 100 and 200 mgms. of urea per 100 c.c. of blood.

The bodily and mental prostration which characterize the earlier stages of asthenic uremia may readily escape detection in animal experiments. For this reason it seemed a matter of some importance to study once again the toxic effects of this compound, using men as the subjects of the study. Our experiments were therefore undertaken with the view to determine whether normal persons manifest toxic symptoms when sufficient urea has been taken by mouth to raise the urea in the blood to the levels encountered in asthenic uremia. Since urea diffuses rapidly from the blood into the tissues it is evident that in order to attain such concentrations in the blood large quantities of urea must be given. Furthermore, since urea is rapidly eliminated from the body by way of the urine, it is evident that the large quantity of urea must be taken within a brief period of time and that prolonged experiments can be carried out only with considerable difficulty. As will appear in the following experiments, the ingestion of 100 grams of urea within a few hours raises the level of blood urea in a normal individual to from 150 to 245 mgms. per 100 c.c. Such concentrations are comparable with those encountered in the asthenic type of uremia, and if the symptoms in the latter condition are in any way dependent upon the concentration of urea in the blood, symptoms should occur under the conditions of our experiment.

Outline of Experiments. Five experiments were performed, four upon the authors themselves and one upon Dr. F. N. Wilson, who volunteered for this purpose. The subject of the experiment presented himself to the clinical laboratory after his usual breakfast and emptied his bladder. The urea content of his blood was determined and this was compared with the output of urea in the urine

by the method of Ambard.[7] The subject then took the urea dissolved in water, either in a single or in divided doses over a period of from three to six hours. In three instances the intake was completed before the noon meal, while in two others one or more doses were taken after the meal. The successive specimens of urine were collected, measured and analyzed for urea over a period varying from nine to thirty hours after the beginning of the experiment. The concentration of urea in the blood and the Ambard coefficient were determined on two or more occasions during the afternoon of the experimental day and once on the following morning. No restriction was placed on the exercise taken, the amount of water drunk, or the amount or kind of food eaten.

The quantity of urea in the blood and urine was determined by Van Slyke's urease method. In the earlier experiments the final titrations were performed, using alizarin monosulphate as an indicator. At the suggestion of H. H. Willard, however, methyl red was used as an indicator in one experiment (No. 2) and was found to give a more definite end reading. The hemoglobin in each specimen of blood drawn was determined by the Autenriech colorimeter.

Observations. The results of our observations are shown in Tables I to V.

Effect on Urea Content of the Blood and Urine. During these observations the amount of urea taken varied from 100 to 125 grams. In the first experiment 100 were taken within fifteen minutes, in the second 125 grams were taken in 25-gram doses at hourly intervals, in the third and fourth 100 grams were taken in a similar manner, while in the fifth experiment 110 grams were taken during six hours, the major portion being taken during the first three hours.

The effect of the ingestion was apparent in the first specimen of urine subsequently passed. This showed a more rapid diuresis and an increased excretion of urea. The rate of excretion rapidly augmented and reached a maximum within a few hours after the last dose had been taken. It was evident, therefore, that absorption from the gastro-intestinal canal was very rapid. At the height of the experiment the maximum rate of elimination of urea varied in the different experiments from 11 to 14.8 grams of urea per hour.

TABLE I.—EXPERIMENT 1 (A. W. H.), DECEMBER 23, 1915

Time.	Urea taken, gms.	Urine, c.c.	Rate of diuresis per 24 hrs.	Gms. of urea per 100 c.c. urine.	Urea excretion.	Rate of urea excretion per 24 hrs.	Urea in blood.	Ambard.	Hb., per cent.	Remarks.
9.26–10.02 A.M.	..	21.8	870	3.02	0.66	26.4	0.040[1]	0.074	93	Considerable nausea.
10.05–10.18	100									
10.02–10.37	..	77.7	3,200	2.37	1.84	75.8	0.072			
10.37–11.09	..	230.0	10,350	2.44	5.61	252.54	0.147	0.093	87	11 A.M. Slight headache; stupor; sleepy; nausea less.
11.09–11.29	..	134.0	9,650	2.50	3.35	241.25	0.166	..	..	11.12 A.M. Headache; dizzy. 11.15 A.M. Headache worse; blood-pressure, 120 85.
11.29–12.02 P.M.	..	240.0	10,470	2.66	6.38	278.5	0.200	0.118	77	11.30 A.M. Headache; dizzy. 11.36 A.M. Soft stool; weak; dizzy. 11.57 A.M. Headache.
12.02–12.30	..	158.0	8,130	2.56	4.04	208.0	0.167	..	..	12.30 P.M. Diarrheal stool; better, but still headache.
12.30– 1.00	..	192.0	9,220	2.96	5.68	272.9	0.193	..	..	1 P.M. Headache and weak.
1.00– 1.30	..	127.0	6,100	3.35	4.24	204.0	0.168			
1.30– 2.07	..	161.0	6,270	3.77	6.07	236.4	0.160	0.107	72	Feels fairly comfortable but unable to work.
2.07– 3.10	..	267.0	6,100	3.52	9.40	215.0	0.167	..	..	Unable to do customary work during the late afternoon.

[1] When the urea in the blood was determined it is followed by an Ambard factor. The remaining figures were interpolated by the method described in the text.

TABLE II.—EXPERIMENT 2 (A. W. H.), APRIL 17, 1916

Time.	Urea taken, gms.	Urine, c.c.	Rate of diuresis per 24 hrs.	Gms. of urea per 100 c.c. urine.	Urea excretion.	Rate of urea excretion per 24 hrs.	Urea in blood.	Ambard.	Hb., per cent.	Remarks.
9.07– 9.43 A.M.	..	17.5	700	2.82	0.49	19.7	0.036	0.079	..	Slight nausea.
9.45	25									
9.43–10.43	..	134.0	3,220	2.28	3.06	73.3	0.072			Slight nausea.
10.49	25									
10.43–11.43	..	155.0	3,720	3.14	4.87	116.9	0.110			
11.47	25									
11.43–12.43 P.M.	..	202.0	4,850	3.24	6.55	157.1	0.142	..	..	12.25 P.M. Slight headache; rumbling in intestines.
12.47	25									
12.43– 1.50	..	267.0	5,740	3.38	9.03	194.0	0.173	..	..	12.50 P.M. Diarrheal discharge; headache worse; some dizziness and apathy; disinclined to work. 1.15 P.M. Headache and apathy. 1.33 P.M. Headache better; apathy continues; slight drowsiness; little dizzy; weak.
1.52	25									
1.50– 2.23	..	205.0	8,950	2.95	6.05	264.0	0.210	..	..	1.52 P.M. Considerable apathy and stupor; headache gone. 2.08 P.M. Dizzy; speech thick; difficult to say words distinctly.
2.23– 2.59	..	251.0	10,040	2.62	6.57	262.6	0.214	0.130	83	2.50 P.M. No headache or dizziness; much apathy and inability to work.
2.59– 3.59	..	351.0	8,420	3.12	10.95	262.7	0.215	..	..	3.05 P.M. Apathetic and tired. 3.40 P.M. Apathetic and dull.
3.59– 4.35	..	197.0	7,880	4.04	7.96	318.4	0.240	..	..	4.00 P.M. Little headache; no energy; feeling better.
4.35– 5.11	..	150.0	6,000	3.90	5.85	214.0	0.192	0.117	85	4.35 P.M. As above.
5.11– 6.40	..	266.0	4,300	3.56	9.48	153.4	0.156	..	..	6.00 P.M. Feeling fairly well.
6.40– 8.36	..	285.0	3,530	4.20	11.97	148.5	0.154	..	..	7.30 P.M. Same.
8.26– 1.40	..	495.0	2,340	4.08	20.20	95.5	0.117			
1.40– 5.20 A.M.	..	305.0	1,990	2.98	9.09	59.4	0.082			
5.20– 7.45	..	215.0	2,130	3.72	8.00	79.4	0.091	..	..	Morning work went slowly; otherwise felt well,
7.45– 9.37	..	140.0	1,800	3.79	5.31	68.2	0.079			
9.37–10.13	..	50.0	2,000	3.84	1.92	76.8	0.084	0.086		
10.13– 1.00 P.M.	..	146.0	1,260	3.69	5.39	46.6	0.083			
1.00– 2.55	..	61.5	770	3.05	1.87	23.5	0.040			

TABLE III.—EXPERIMENT 3 (Q. O. G.), DECEMBER 27, 1915

Time.	Urea taken, gms.	Urine, c.c.	Rate of diuresis per 24 hrs.	Gms. of urea per 100 c.c. urine.	Urea excretion.	Rate of urea excretion per 24 hrs.	Urea in blood.	Ambard.	Hb., per cent.	Remarks.
10.20–10.56 A.M.	..	33.0	1,320	2.51	0.83	33.1	0.043	0.075	95	Weight 177 lbs.
11.00	25									
10.56–12.26 P.M.	..	231.0	3,700	3.04	7.02	112.5	0.098	..	..	11.38 A.M. Slight nausea; slight headache; dizzy. 11.45 A.M. Better.
12.00 M.	25									
12.26– 1.44	..	280.0	5,170	3.52	9.82	182.7	0.153	..	..	12.37 P.M. Headache; sleepy; some dizziness; somewhat unsteady when attempting to walk or work with hands.
1.00 P.M.	25									
1.44– 2.15	..	154.0	7,150	4.02	6.17	287.4	0.222	..	..	1.30 P.M. No nausea; more headache; dull; somnolent. 1.40 P.M. Dull headache; some throbbing in ears and head; stupid.
2.00	25									
2.15– 2.51	..	193.0	7,720	4.05	7.80	312.9	0.245	0.122	90	2.15 P.M. Headache worse; no nausea; dizziness about the same.
2.51– 3.40	..	221.0	6,490	4.34	9.59	281.6	0.231			2.54 P.M. No nausea; dull frontal headache; effort to concentrate; sleepy.
3.40– 4.36	..	261.0	6,710	4.00	10.44	268.4	0.218			3.40 P.M. Headache no worse, but more stupid and sleepy; difficult to do any work.
4.36– 5.22	..	186.0	5,820	4.99	9.27	290.5	0.236			5.10 P.M. Dull headache; restless and irritable; weight 170 lbs.
5.22– 6.04	..	154.0	5,280	4.03	6.20	212.8	0.187	0.115	81	5.30 P.M. Headache began to go away, but still an effort to concentrate and to do any work.
6.04– 7.48	..	238.0	3,290	5.32	12.66	175.4	0.181			6.30 P.M. Excessively irritable, but mental processes are slow.
7.48–10.50	..	396.0	3,130	4.75	18.75	148.4	0.156			
10.50– 2.35	..	345.0	2,210	4.13	14.25	91.3	0.114			
2.35– 8.25	..	287.0	1,180	5.64	16.20	66.6	0.099			
8.25–10.43	..	78.0	814	6.43	5.01	52.4	0.085			
10.43–11.22	..	18.5	683	6.12	1.13	41.8	0.074	0.092	94	
11.22– 3.45	..	131.0	717	4.84	6.35	34.7	0.062			

TABLE IV.—EXPERIMENT 4 (A. D. W.), JANUARY 3, 1916

Time.	Urea taken, gms.	Urine, c.c.	Rate of diuresis per 24 hrs.	Gms. of urea per 100 c.c. urine.	Urea excretion.	Rate of urea excretion per 24 hrs.	Urea in blood.	Ambard.	Hb., per cent.	Remarks.
8.30– 9.08 A.M.	..	90.0	3,420	1.20	1.08	41.0	0.040	0.075	93	Weight, 141¾ pounds.
9.15	25	..	..	..	..	..	..	..	..	9.15 A.M. Nausea, passing off in a few minutes.
9.08– 9.44	..	474.0	18,960	1.20	5.7	227.5	0.103			
10.15	25									
9.44–10.56	..	384.0	7,680	2.50	9.6	192.2	0.128	..	..	10.40 A.M. Feels uneasy; slight headache passing off in a few minutes.
11.15	25									
10.56–12.08 P.M.	..	323.0	6,460	2.91	9.4	187.9	0.149	..	..	11.25 A.M. Rather dopy; head not clear; blood-pressure, 130–94; no nausea.
12.15	25									
12.08–12.27	..	91.0	6,890	3.24	2.9	223.2	0.180	..	..	12.15 P.M. Headache and dizziness; sleepy.
12.27– 1.03	..	171.0	6,840	3.37	5.7	230.7	0.193	0.118	87	12.45 P.M. Feels better now.
										12.50 P.M. Lunch; appetite good; nervous; hands unsteady.
1.03– 2.15	..	391.0	7,820	3.84	15.0	300.3	0.223	..	..	1.25 P.M. Dizzy; hands and feet unsteady; head feels heavy.
										2.15 P.M. Dizzy and unsteady.
2 15– 3.27	..	359.0	7,180	3.60	12.9	258.5	0.203	..	..	3.00 P.M. Tired physically and mentally; effort required to accomplish anything.
										3.15 P.M. Blood-pressure 130–86.
3.27– 4.39	..	333.0	6,660	3.24	10.8	215.8	0.177	..	..	4.15 P.M. Head still aches; intellect cloudy; thinks slowly; dizziness less marked; feet heavy and drag.
4.39– 5.15	..	314.0	12,560	2.04	6.4	256.3	0.170	0.112	75	
5.15– 5.51	..	222.0	8,880	2.16	4.8	191.8	0.150	..	..	5.40 P.M. Weight, 142¼ pounds.
5.51– 6.35	..	270.0	8,840	1.88	5.1	166.4	0.132	..	..	6.15 P.M. Headache and tired.
6.35–11.00	..	920.0	5,000	2.66	24.4	133.0	0.125			
11.00– 8.00	..	556.0	1,480	4.36	24.2	64.5	0.094			
8.00–10.05	..	133.0	1,530	4.36	5.8	66.7	0.090			
10.05–11.09	..	235.0	5,290	1.51	3.5	79.9	0.076			
11.09–11.45	..	161.0	6,440	0.98	1.53	63.4	0.059	0.094	86	

TABLE V.—EXPERIMENT 5 (F. N. W.), JANUARY 10, 1916

Time.	Urea taken, gms.	Urine, c.c.	Rate of diuresis per 24 hrs.	Gms. of urea per 100 c.c. urine.	Urea excretion.	Rate of urea excretion per 24 hrs.	Urea in blood.	Ambard.	Hb., per cent.	Remarks.
8.42– 9.18 A.M.	..	35.5	1,420	2.66	0.9	37.8	0.036	0.058	95	
9.30	25									
9.18–10.30	..	183.0	3,660	2.74	5.1	100.3	0.063	..	..	9.30 A.M. Feel well.
										9.40 A.M. Head a little thick.
10.25	25									
10.30–11.16	..	173.0	5,410	4.13	7.1	223.5	0.111			11.45 A.M. Head a little thick; otherwise well.
11.30	20									
11.16–12.16 P.M.	..	230.0	5,520	4.42	10.1	243.9	0.122			
12.30	10									
12.16– 1.00	..	197.0	6,450	5.52	10.9	355.9	0.163	..	..	12.30 P.M. Little weak and thick-headed.
										12.35 P.M. Weak and slightly drowsy.
										12.52 P.M. Less sleepy.
1.30	10									
1.00– 1.48	..	181.0	5,430	4.33	7.8	235.1	0.128			1.48 P.M. Feels well.
2.30	10									
1.48– 2.49	..	248.0	5,860	4.03	10.0	236.4	0.133			
2.49– 3.29	..	181.0	6,510	4.18	7.6	272.1	0.150	0.079	85	3.25 P.M. Slight headache.
3.30	10									
3.29– 4.19	..	225.0	6,480	3.89	7.7	252.1	0.138	..	..	4.02 P.M. Headache.
4.19– 4.59	..	179.0	6,440	4.14	7.4	266.6	0.141			
4.59– 6.33	..	367.0	5,620	3.67	13.3	205.3	0.117			
6.33– 8.28	..	422.0	5,380	3.89	16.4	209.5	0.114	..	..	Headache increased until 8.30 A.M., at which time it was quite severe; went to sleep and headache passed off during the night.
8.26– 6.30 A.M.	..	684.0	1,640	5.83	39.9	95.6	0.091			
6.30– 9.20	..	132.0	1,120	5.32	7.0	59.6	0.044			
9.20– 9.45	..	23.0	1,320	5.57	1.3	73.5	0.045			
9.45–10.21	..	34.0	1,360	4.54	1.5	61.7	0.039	0.042	95	

From this maximum the rate of elimination fell, at first rapidly and then more slowly. At the end of twenty-four hours it had approached but had not reached the original rate. The amount of urea excreted within the twenty-four hours was greater than the amount ingested, but in view of the fact that the urea level in the blood had not yet returned completely to the normal at this time it is fair to assume that the amount excreted in the twenty-four hours was somewhat less than the sum of what had been ingested and what had been formed in the body during this time.

The amount of urea in the blood as determined by direct analysis also reaches a maximum within a few hours after the last dose had been taken. This maximum varied from 150 to 245 mgms. per 100 c.c. of blood, indicating that we had attained our object of increasing the concentration of urea in the blood to amounts that were comparable with those encountered in the asthenic type of uremia.

According to Ambard there exists, for any individual, a constant relation between the concentration of urea in the blood and its excretion in the urine. Ambard's formula is as follows:

$$k = \frac{U}{\sqrt{D}\sqrt{C/25}}$$

where U represents the grams of urea in 1000 c.c. of blood, D the output of urea over the observed period calculated for twenty-four hours, and C the concentration of urea in the urine excreted, expressed in grams per liter. In the above experiments the Ambard factor k was determined for each specimen of blood drawn. It was found to vary far less than any of the other data that enter into it, *i. e.*, the concentration of urea in the blood, the rate of excretion of urea, and the diuresis. Nevertheless the factor did not remain constant in any of the experiments, but regularly showed a rise when the urea concentration in the blood rose and a fall when the urea concentration in the blood fell. One might be inclined to interpret the rise of the Ambard factor during our experiments as an indication of renal fatigue owing to the extraordinary strain placed upon the kidney in the way of excreting urea. Against this interpretation, however, is the fact that the Ambard factor regularly fell during the afternoon of the experiment, although one would expect that here if anywhere the kidney would show signs of fatigue owing to the

continued excessive work. It seems to us probable, therefore, that the Ambard "constant" is but an approximation to the actual facts and that the kidney does not work with the mathematical precision that might be assumed from such a formula.

Nevertheless we found the Ambard formula of considerable service in that by this means we were able to estimate the approximate concentration of urea in the blood at numerous points of our experiment. These estimations were made as follows: The determined points on the Ambard curve were connected by straight lines and the Ambard factor was assumed to correspond to the point at which these connecting lines crossed the time intervals. Having this assumed constant and knowing the rate of diuresis and the rate of urea elimination in the urine, it became possible to estimate the approximate level of urea in the blood according to the following transposition of the Ambard formula:

$$U = k\sqrt{D\sqrt{C/25}}$$

where the letters have the same significance as in the original formula. In this way the approximate level of blood urea could be interpolated at numerous points during an experiment. In the charts these interpolations may be recognized by the fact that they are not followed by an Ambard factor. The advantage of such interpolations is at once obvious when one endeavors to compare the onset and duration of symptoms with the concentration of urea in the blood at different times during an experiment.

Effect on Water Metabolism. No restriction of fluid intake was carried out in these experiments, and with one exception (Experiment 3) the fluid intake was not recorded. Although it was not possible to follow accurately the water metabolism in the body, nevertheless our observations indicate that the ingestion of such large quantities of urea is not without an effect upon the fluids of the body. Considerable thirst was experienced during and for a time after the ingestion of the urea and as the subjects were allowed to drink freely considerable water was taken to satisfy this thirst. At the same time a marked diuresis accompanied the elimination of the large quantities of urea. The body weight varied according to the balance between the intake and the output of fluid. In Experiment

4 the subject drank very large quantities of water and gained ½ pound during the day and lost 1½ pounds during the following night. In Observation 3, the subject lost 7 pounds between the onset of the experiment and 5 o'clock in the afternoon. In Experiment 2, 4 pounds was lost in twenty-four hours, and the original weight was not recovered for about four days. The changes in body weight were not recorded in Experiments 1 and 5.

During each experiment there occurred a definite fall in the hemoglobin, as is shown in the following table.

TABLE VI.—EFFECT ON THE HEMOGLOBIN

Experiment.	Hemoglobin before.	Hemoglobin after. Same day.			Next morning.
1	93	87	77	72	92
2	93	83	85		
3	95	90	81	..	94
4	93	87	75	..	86
5	95	85	..	..	95

This fall was usually most pronounced late in the afternoon of the experimental day, when the concentration of urea in the blood had already begun to fall. On the following morning the hemoglobin had returned more or less completely to the normal. Such a transient reduction in the hemoglobin indicates a dilution of the blood, and since it may occur even when the subject was rapidly losing weight (Experiment 3) the necessary liquids in such a case must have been withdrawn from the tissues. This dilution of the blood during the diuresis following these excessive quantities of urea is perhaps comparable to that which may occur after the ingestion of sodium chloride or the saline diuretics. It probably played some part in provoking the diuresis in our experiments.

THE SYMPTOMS. Each subject noted his symptoms as they occurred. By comparing these notes with the concentration of urea in the blood at the time, it was possible to add to the objective character of the observations and to determine to what extent the symptoms corresponded with an augmented concentration of urea in the blood. Experiment 5 differed from the first four, partly because the urea concentration did not reach the same high level and partly because the symptoms were less marked and not so definitely related to the maximum concentration of urea in the blood. For this reason it will be considered separately.

In all of the first four experiments some nausea was experienced after taking the first dose of urea, but vomiting did not occur. The nausea was most marked in Experiment 1, where 100 grams of urea were taken within fifteen minutes. In Experiment 2 it was present after the first three doses and was absent after the last two. In Experiments 3 and 4 slight nausea was experienced after the first dose but none after the next three. In all cases the nausea had disappeared before the concentration in the blood had reached its maximum. It is evident, therefore, that in these experiments the nausea did not depend upon a high concentration of urea in the body fluids or tissues but was probably associated with local changes in the gastro-intestinal canal. The subject of Experiments 1 and 2 had diarrheal evacuations of the intestines a few hours after the ingestion of the urea. The other subjects experienced no intestinal disturbances.

In each of the first four experiments definite symptoms occurred at the time that the concentration of urea in the blood was highest. Headache was first noted, the sensation usually being described as a tight feeling in the head or as a dull ache. This headache was soon followed by dizzy sensations which were in turn followed by apathy, drowsiness and an inability to do the customary amount of work. Feelings of bodily fatigue and weakness occurred in each case. The subjects of Experiments 3 and 4, upon whom fell the burden of the chemical determinations, were in each case unable to carry on this work during the afternoon which followed the taking of the urea by reason of mental and bodily fatigue together with an inability to concentrate the attention. In both instances the hands were unsteady. The subject of Experiment 3 became excessively irritable during the afternoon, while the subject of Experiment 4 complained particularly of bodily fatigue. In Experiment 2 at the height of the intoxication the subject found some difficulty in pronouncing words distinctly.

These cerebral and bodily symptoms were most pronounced at the time of maximum concentration of urea in the blood. In all cases they appeared in a definite form at about the time that the blood urea reached a concentration of 150 to 160 mgms. per 100 c.c. It is noteworthy that they appeared to be less intense at corresponding

levels during the afternoon when the amount of urea in the body was lessening.

The subject of Experiment 5 did not show as high a concentration of blood urea as did the other subjects. This was due in part to the fact that his ingestion of urea extended over a longer period. In part it was due to the fact that he showed an unusually rapid excretion with an unusually low Ambard coefficient (increased renal permeability to urea). The subject complained at first of feeling somewhat thick-headed and later of being somewhat drowsy and disinclined to work. The latter symptoms coincided with the maximum concentration of urea in his blood (163 mgms.). During the afternoon a headache developed which gradually became more marked as the afternoon advanced and was quite intense at bedtime. During the night it disappeared. This subject suffers from occasional headaches (migraine?) and the experiment seems to have induced a headache of the usual type but of unusual severity. This headache was not due directly to the high concentration of urea in the blood, for it reached its maximum after the concentration in the blood had fallen below 114 mgms.

In two experiments (1 and 4) the blood-pressures were taken at the height of the intoxication, but in neither case was any marked hypertension present.

The symptoms observed at the maximum concentration of urea in the blood during our experiments correspond almost exactly with those described by Reiss for the asthenic type of uremia, *i. e.*, drowsiness and indifference, bodily fatigue and prostration. The loss of appetite described by Widal did not occur. On the other hand, headache and dizziness were quite constant. The symptoms observed developed at approximately the same level of blood urea in all subjects and this level corresponded roughly to that which is associated with definite and unmistakable symptoms in asthenic uremia.

To the analogy that has been drawn between the symptoms observed in these experiments and those of asthenic uremia, the objection might be raised that the symptoms observed after ingestion were due to the rapid entrance of urea into the tissues and that had the high level been maintained for some time the symptoms

would have disappeared. This criticism is supported by the fact that the symptoms were usually more marked at a given level of urea in the blood when the urea was accumulating in the body than they were at the same level of blood urea when the urea in the body was lessening. It seems probable, therefore, that a portion of the symptoms observed may have been due to the acute character of the experiment. Nevertheless the following facts indicate that the high level of urea in the body was responsible for the major portion of the symptoms: (1) No definite symptoms occurred while the blood was rising from 40 to 150 mgms. per 100 c.c. nor have symptoms been observed by other observers when 20 to 30 grams of urea have been given in a single dose; (2) the onset of symptoms occurred in each of our subjects when the level of blood urea had passed a definite point (about 150 mgms.); (3) the symptoms, though less marked, persisted until the blood urea had fallen to approximately 160 mgms. per 100 c.c. For these reasons we believe that the symptoms in our experiments were due in the main not to the sudden entrance of urea into the tissues but to its high concentration therein.

It seems probable therefore that, when as a result of nephritis, the blood urea exceeds a concentration of 150 mgms. per 100 c.c. the symptoms of bodily and mental asthenia may be explained in part as being due to the high concentration of urea in the body fluids and tissues. This by no means excludes the possibility that other substances may play a role in producing the symptoms of this type of uremia and, indeed, the fact that animals die only when extraordinary doses of urea are administered suggests that the fatal outcome of asthenic uremia in man may be due to other substances than urea.

Distribution of Urea to the Tissues. It is well known that urea diffuses readily between the blood and the tissues. This fact is also apparent in our experiments. Assuming, for example, that there are 5 liters of blood in the body and that all of the urea administered remained in the blood, it would require but 10 grams of urea to give a concentration of 200 mgms. per 100 c.c. of blood. Since approximately 100 grams of urea taken by mouth were required to raise the blood urea to this level it is evident that the major portion

of the urea absorbed from the gastro-intestinal canal must have passed rapidly from the blood into the tissues.

One may estimate roughly the additional amount of urea in the body at any time during our experiments, for this will equal the amount absorbed from the intestinal canal plus that formed by metabolism in the body and minus that eliminated through the excreta. For purposes of calculation we have assumed (1) that the urea was completey absorbed from the intestinal canal, (2) that it was eliminated entirely by way of the urine, and (3) that the rate of metabolism was such that $1\frac{1}{2}$ grams of urea were formed hourly in the body. If these assumptions are made, then the total amount of urea in the body at any time during the experiment may be estimated. Such estimations are shown in the following table:

TABLE VII.—EXCESS UREA IN THE BODY AND ITS RELATION TO THE EXCESS IN THE BLOOD

Experiment.	Body weight.	Time since first determination.	Excess urea in body. (*a*)	Excess in blood. (*b*)	Relation. (*a*) (*b*) (*c*)
1	75 kgs.	2 hrs.	89 gms.	160 mgms.	1.8
		4 hrs.	72 gms.	120 mgms.	1.7
2	75 kgs.	5 hrs.	98 gms.	178 mgms.	1.8
		$7\frac{1}{2}$ hrs.	77 gms.	156 mgms.	2.0
3	80 kgs.	4 hrs.	79 gms.	202 mgms.	2.8
		7 hrs.	47 gms.	144 mgms.	3.1
4	65 kgs.	4 hrs.	76 gms.	153 mgms.	2.0
		8 hrs.	36 gms.	130 mgms.	3.6
5	78 kgs.	6 hrs.	54 gms.	113 mgms.	2.1

The various possible errors in the assumption upon which these calculations are based do not permit one to draw any definite conclusion as to the exact relation that exists between the amount of urea in the body and its concentration in the blood. It should be noted, however, that in the first two experiments diarrheal discharges occurred and that in this way a certain amount of urea was probably lost from the body. If this were the case, the estimated amount of urea in the body would have been less and the relation (*c*) would have been greater. Similarly, in Experiment 5 and in the first estimation of Experiment 4 the blood was drawn about half an hour after the last dose of urea had been given. If one were to assume that this had not been entirely absorbed, the excess in the body would again be less and the relation (*c*) greater. It would appear, therefore, that for every gram of excess urea in the body

the concentration of urea in the blood rose at least 2.5 mgms. per 100 c.c. of blood.

If 1 gram of urea be uniformly distributed in a body weighing 70 kilos, it would cause an increase of concentration amounting to 1.4 mgm. per 100 grams. It is evident, therefore, that while the major portion of the urea ingested entered the tissues, its concentration in the body as a whole fell considerable short of its concentration in the blood. Marshall and Davis have shown from chemical analyses that the urea concentration in various organs and tissues of the body is approximately equal to its concentration in the blood. They found, however, that in the case of fat the urea concentration was low, and it seems probable that the same is true of the bones, the cartilages and possibly of other tissues. Possibly if one could allow for the low percentages in such tissues the urea concentration in the remaining tissues of our subjects may have approached that of the blood.

Conclusions. 1. By giving approximately 100 grams of urea by mouth over a short interval of time, it is possible to increase the concentration of urea in the blood of normal individuals to levels of 160 to 245 mgms. per 100 c.c.

2. At such levels of blood urea definite symptoms occur. These consist of headache, dizziness, apathy, drowsiness, bodily weakness, and fatigue.

3. These symptoms are comparable to those encountered in the asthenic type of uremia.

4. For every gram of excess urea in the body there is a rise of concentration in the blood which approximates 2.5 mgms. per 100 c.c.

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DISCUSSION

Dr. Warren Coleman, New York, said an instructive case was that of a girl, aged thirteen years, who came to the hospital in uremic convulsions. Blood taken for therapeutic purposes contained a total of 20 mg. per 100 c.c. of non-coagulable nitrogen. In later convulsions the non-coagulable nitrogen was never above 30 mg. per 100 c.c. of blood. It is evident that in some cases urea is not a factor in the convulsions.

Dr. L. G. Rowntree, Minneapolis, referred to the case of a man with convulsions, concerning the cause of which opinion was divided between cerebral arteriosclerosis and eclamptic uremia: The renal functional studies did not indicate uremia, and autopsy revealed the cause to be cerebral disease. In the absence of accumulation of nitrogenous waste products in the blood, some cause other than renal insufficiency should be sought for convulsions, coma, etc. Organic changes in the brain will be frequently found.

Dr. Henry A. Christian, Boston, said Dr. Hewlett's observations are important. They coincide with his own observation of the non-effect of diuretics on the removal of nitrogen and of their failure to influence the symptoms of uremia. It is necessary to consider both blood and body accumulation of nitrogen and kidney excretion of nitrogen in these problems; storage is the factor rather than the amount in the blood. How long did it take for the level of blood urea to return to normal?

Dr. Chas. S. Bond, Richmond, Ind., asked Dr. Hewlett whether diuresis followed the ingestion of the urea and how much water was taken during the experiments.

Dr. A. W. Hewlett, Ann Arbor, said it is necessary to keep in mind that more substances are concerned in uremia than urea. Thus, Foster has demonstrated the presence of a definite toxic base in the blood of those suffering from the epileptiform type of uremia. In our experiments the time at which the urea level of the blood returned to normal was not ascertained. The observations were not continued long enough to observe this return. The symptoms lasted five hours or more. The concentration of urea in the body as a whole was considerably less than its concentration in the blood (about 50 per cent.). There was an enormous diuresis, which was shown to be independent of water intake in 1 case.

EXPERIMENTAL ENDOCARDITIS: ITS PRODUCTION WITH STREPTOCOCCUS VIRIDANS OF LOW VIRULENCE

By H. K. DETWEILER, M.B.

AND

W. L. ROBINSON, B.A., M.B.

TORONTO

In October, 1915, there was reported from this laboratory and the Department of Medicine[1] results obtained by the special methods of Rosenow in connection with an investigation into the bacteriology of the blood in a form of endocarditis less severe than the type commonly called subacute bacterial endocarditis, and in many cases milder even than those commonly recognized as simple endocarditis. We promised at that time to publish an account of the characteristics of the organisms recovered and their action upon animals. In the pursuit of this work we were hampered greatly by the special conditions made necessary by the exigencies of the war, particularly in regard to the depletion of the staff of the laboratory in response to the call to overseas service. Many phases of the work, therefore, have been allowed to remain untouched until time permits of their further investigation, but sufficient data is at hand to warrant the publication of our findings.

In following out the methods advocated by Rosenow[2] we have elaborated a technic which has been used for some time, and which has given splendid results.

[1] Oille, Graham and Detweiler, Streptococcus Bacteremia in Endocarditis, Jour. Am. Med. Assn., October 2, 1915.

[2] The Newer Bacteriology of Various Infections as Determined by Special Methods, Jour. Am. Med. Assn., September 12, 1914, p. 903.

Thirty c.c. of blood are withdrawn into a Record syringe, which has previously been sterilized and loaded with 5 c.c. of sterile 2 per cent. sodium citrate solution in normal saline. By inverting the syringe several times a thorough mixture is secured and clotting thereby prevented. The citrated blood is directly transferred to eight centrifuge tubes containing sterile distilled water. The result of this step is the laking of the corpuscles and the liberation of the hemoglobin. These tubes are immediately centrifuged at high speed and the supernatant fluid subsequently pipetted off with a

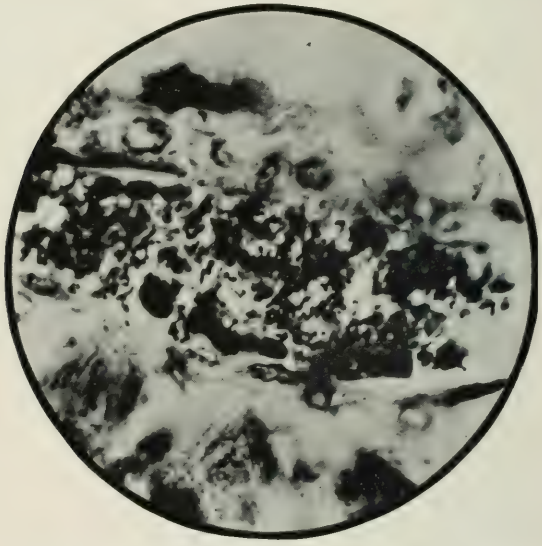

FIG. 1 (R 517).—Bacteria growing in bloodvessel of the myocardium.

sterile pipette attached to a water suction pump. The sediment remaining in the bottom of the tubes is composed of the broken-down hulls of the corpuscles together with any bacteria which may be present. This operation is performed inside a glass cabinet which contains a Bunsen burner, the tube to the suction pump and the tap from the broth reservoir. By merely adding bouillon to the sediment, each centrifuge tube is converted into a culture flask, and is now ready to be placed in the incubator. The sediment of two tubes is reserved to be mixed with ascitic agar for anaërobic conditions. This is obtained in a satisfactory manner by making this mixture

after the agar has cooled to 40° C., and pouring into a tall test-tube, the result being almost complete anaërobiosis at the bottom and a varying oxygen gradient as the top is approached. The disadvantages of this method of blood culture are probably confined to two: The first is the time and skill required to carry out the technic, and this precludes its use as a routine measure. Such an objection, however, is not valid in a research laboratory. The second disadvantage is the large amount of unavoidable manipulation. Our only answer to that is the absence of contamination

FIG. 2 (R 968).—Valvular vegetation.

which has given us the confidence we have in our results. The advantages are three: First of all it seems reasonable that in a case in which the number of bacteria in the blood are few, the larger the sample taken, the more chance of obtaining the organism. Secondly, in chronic cases, such as we are investigating, it is believed that the patient has developed a certain amount of immune bodies in his serum. The provision in this method for the discarding of this immune serum will insure the organism having as little as possible to contend with. The serum removed is replaced by ascitic fluid from a patient who may reasonably be considered not to have

an immunity to a streptococcus infection. In this way our medium is enriched by the necessary serum proteins without the danger of including inhibiting bodies. Lastly, the hemoglobin, which is said to have a detrimental effect upon certain strains of streptococci, is largely removed.

The organisms used in this series of experiments were obtained from the blood from cases of subacute and chronic infectious endocarditis. All of the strains belong to the family of Streptococcus viridans, that is to say, while not all of them produced a distinct green on blood agar, they resembled each other in their action upon the various sugar media and in their low grade of virulence. The minority, which were not green-producing, yielded grayish, fairly adherent colonies on blood agar, a few produced a brown color. All grades of chain formation, from very short to quite long forms, were found among them. They were usually arranged in pairs throughout the chain. They did not dissolve in bile salts. None of them fermented inulin. All produced acid and coagulation in lactose, maltose and levulose serum water. All but two acted in the same manner on saccharose. Fifty per cent. fermented salicin. Mannit, asparagin, as well as inulin, remained unchanged. The organisms are difficult to keep in stock, requiring to be transferred every two or three days. This is due to the inhibitory action of the acid which they produce on the glucose broth or agar used, the acidity going as high as 3 per cent., whereas the reaction of the media upon which they are planted should not be higher than + 0.5. Latterly we have been making up the broth for stock cultures with 1 per cent. calcium carbonate, which insures the neutrality of the medium and on this the organism lives for about seven days.

TABLE I

Strain.	Lactose.	Levulose.	Saccharose.	Maltose.	Inulin.	Raffinose.	Mannit.	Asparagin.	Salicin.
R 15–15	+	+	−	+	−	−	−	−	−
R 15–14	+	+	+	+	−	−	−	−	−
R 15–55	+	+	−	+	−	−	−	−	−
R 15–11	+	+	+	+	−	+	−	−	+
R 15–12	+	+	+	+	−	−	−	−	+
R 15–50	+	+	+	+	−	−	−	−	+
R 15–F	+	−	+	+	−	−	−	−	−
R 15–Y	+	+	+	+	−	−	−	−	−
R 15–B	+	+	+	+	−	+	−	−	+
R 15–P	+	+	+	+	−	−	−	−	−
R 15–A	+	+	+	+	−	−	−	−	+
R 16–131	+	+	−	+	−	+	−	−	−

The animal experiments have been confined to an attempt to produce a condition in the rabbit analogous to that of the patient from whom the organism was obtained. The great difficulty of producing endocarditis experimentally, without previous injury to the valves, is well known. After unsuccessful attempts had been made, several observers succeeded in producing the condition by adding to the emulsion of organisms injected a mechanical irritant. Among those investigators were Hibbert,[1] who added potato particles, Orth and Wyssowitsch,[2] and Fulci,[3] who used pulverized

FIG. 3 (R 664).—Focal lesion in myocardium. Note bloodvessel plugged with bacteria.

charcoal. These foreign bodies produced a condition of erosion upon the valve cusps, which thereupon became a favorable soil for the inflammation of the organism. Lissauer,[4] Horder[5] and Rosenow[6] and others have succeeded in producing endocarditis in rabbits

[1] Fortschritte der Medicin, 1886, iv, p. 1.
[2] Virchows Archiv, 1886, ciii, pp. 300 and 333.
[3] Beiträge z. Path. Anat., 1908, xliv, p. 349.
[4] Cent. f. allg. Path., etc., 1912, xxiii, p. 243.
[5] Quarterly Journal of Medicine, 1902, ii, p. 289.
[6] Journal of Infectious Diseases, 1909, vi, p. 245; 1910, vii, pp. 411, 429; 1912, ii, p. 210; Jour. Am. Med. Assn., November 13, 1915.

without the aid of foreign irritants. The condition of course is produced with less difficulty with organisms of definite virulence. All are agreed upon the fact that the streptococcus obtained in chronic infectious endocarditis is of very low virulence. Rosenow lays special emphasis upon this point. Believing that the strains of streptococci with which we were working were even less virulent than those which this author described, we were anxious to establish conclusive evidence of their ability to produce the disease in animals.

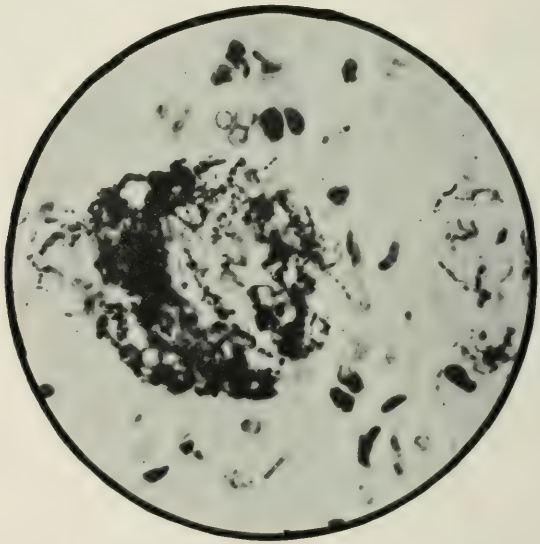

Fig. 4 (R 574).—Bacteria growing in bloodvessel of kidney.

Not only that, but we were equally anxious to prove that these organisms of almost negligible virulence had nevertheless a special affinity for heart valves and myocardium. We feel that the results of our investigations have justified this belief.

The animals used were rabbits, from six weeks to two and a half months old. The majority were Belgian hares. The cultures were grown in vaccine bottles of 60 c.c. capacity, containing about 40 c.c. ascitic glucose bouillon. A copious growth was obtained in twenty-four hours, and the bottle was then centrifuged at high speed in a

special trunnion-cup and the supernatant bouillon pipetted off. This operation can be done with such nicety that practically no free fluid is left with the bacteria, which are thereupon suspended in 2 or 3 c.c. sterile saline solution and injected intravenously into the rabbit. By filling the syringe with the emulsion and expelling it through a small needle the clumps are largely broken up. This is repeated several times and a uniform emulsion results. The marginal vein of the ear was used invariably. Each strain of

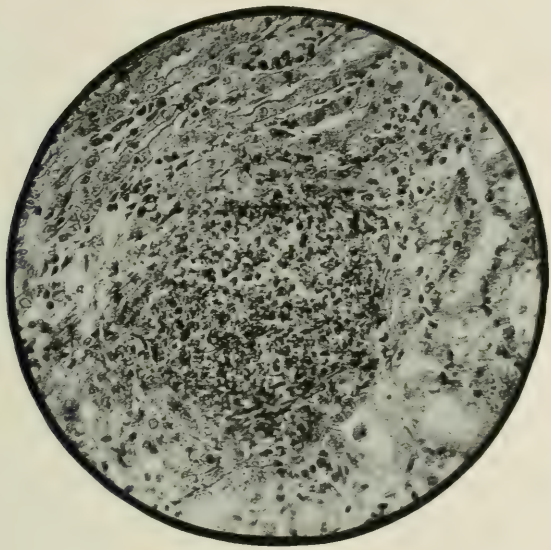

FIG. 5 (R 574).—Focal lesion in kidney.

organism is studied first of all in regard to its virulence. The lethal intravenous dose is roughly estimated by injecting varying amounts of the emulsion into several rabbits. The average dose tolerated is the amount of emulsion obtainable from one to two vaccine bottles. This is an enormous dose of bacteria to be introduced directly into the blood stream of a rabbit weighing, say 700 grams. When the lethal dose and the *dosis tolerata* are established we try to keep the injections up to the highest point possible without killing the animal too quickly.

TABLE II

No. of rabbit.	Strain of organism.	Number and amount of intravenous injection.	Clinical picture.	Death after first inoculation.	Postmortem findings.	Postmortem cultures.
R 333	R. T.	1 V.B.C.	Died in 10 minutes	Ten minutes	Hemorrhage into papillary muscle of right ventricle, otherwise normal	No report.
R 665	R. T.	2 V.B.C.	Temperature of 103.4° three days in succession	11 days	Heart: Tricuspid valve shows large verrucose vegetation, involving 2 cusps, size of a small bean. Photo taken	Cultures: Heart's blood, spleen, liver and pericardium all negative.
R 341	R. T.	4 V.B.C.	Temperature maximum, 104.6; minimum, 102.4	18 days	Heart: three large vegetations on tricuspid valve, white diameter from 3 mm. to 5 mm.: lumen of valve almost completely closed; right auricle dilated; evidences of tricuspid incompetency, hydropericardium, hydrothorax, ascites, kidneys congested, liver congested; mesenteric veins swollen	Cultures from heart's blood: streptococci.
R 97808	15–131	1 V.B.C.	Died during night	A few hours	Pericarditis with effusion; subserous hemorrhage about 1 cm. in diameter, 6 in. from pylorus Section: jejunum shows a hemorrhage into the submucosa and mucosa and formations of fibrin extending into the lumen of the intestine; areas of R. C. infiltration around the hemorrhage	Cultures from heart's blood, lungs, liver, pericardial cavity all yield streptococci.
R 968	15–50	16 small doses; 1 medium, 1 large	Died during night after last dose	133 days	Hemorrhage into base of one cusp of aortic valve; early pneumonia; paraffin section shows vegetation under valve	Culture from spleen, liver, and lungs negative.
R 600	15–55	1 original bouillon; 2 culture bouillon; ½ culture bouillon	After last dose became very ataxic; struggled on the floor; back arched lasted about 5 minutes; respiration rapid	3 days	Hemorrhage in curtain of mitral valve, tiny vegetations near base of mitral valve; joints normal	No report.
R 125	15–55	2 small doses	. . . . .	7 days	No evidence of endocarditis; liver congested; hydropericardium; pericarditis	Cultures from liver, heart's blood, and pericardial cavity gave streptococci.
R 991	15–55 from R. 125	10 small doses and 1 large dose	Last dose 2 V.B.C.; died early next morning	92 days	Heart muscle flabby; heart muscle shows numerous small scattered areas of round-celled infiltration; some perivascular infiltration; kidney focal and diffuse nephritis; numerous circumscribed areas of round-celled infiltration	Cultures from spleen and lung show Streptococcus viridans.

TABLE II (Continued)

No. of rabbit.	Strain of organism.	Number and amount of intravenous injection.	Clinical picture.	Death after first inoculation.	Postmortem findings.	Postmortem cultures.
R 593	15–99	2 small, 1 large, 1 medium	Rabbit very emaciated and weak	46 days	Heart: small hemorrhage into tip of papillary muscle and mitral valve, small atheromatous patch in aortic arch just above aortic valve; two small areas of R. C. infiltration on the surface of one of the valves, one near free margin and other near base of valve; areas of granular degeneration of heart muscle	Culture from liver streptococci.
R 383	R. T.	1–2 V.B.C. 2–1 V.B.C.	Rabbit became very thin	10 days	Heart: Pericarditis endocarditis; two large vegetations on tricuspid valve about the size of a pea, white in color; pink verrucose vegetations superimposed; cordæ tendinæ fibrosed and contracted; white patches on inner wall of right auricle	Cultures from vegetations and heart's blood yield streptococci. See Fig. I.
R 281	A 9071Y isolated from rabbit previously inoculated with strain, 15–131	First culture from heart's blood and pericardium of rabbit, A 9071Y	.....	24 hours	Marked hemorrhage into pericardial cavity; the pericardial surface of the heart dull grayish white; other organs apparently normal	Cultures from pericardial cavity, heart's blood, spleen and liver, yield streptococci.
R 518	Stein	2 medium; 1 V.B.C.	.....	18 days	Liver, spleen, and kidney congested	Cultures from liver, spleen and heart's blood gave streptococci.
R 517	Stein	3 medium doses	Died 15 minutes after last injection	11 days	Heart: Subendothelial hemorrhage in muscle wall and also hemorrhage in one of the papillary muscles of the tricuspid valve; hemorrhage into the mitral valve with a few very fine vegetations along the free margin; heart muscle shows fatty degeneration; scattered throughout are bacteria emboli, some vessels occluded by bacteria emboli or thrombus of bacteria and corpuscles; nodule of round-celled infiltration in mitral valve	Cultures from liver, spleen, and heart's blood gave pure streptococci.
R 521	15–99	3 medium doses	Seven days after last injection killed rabbit; getting very thin	18 days	Heart: small hemorrhage, of a brownish color, in one of the papillary muscles of mitral valve	Cultures from liver, spleen, and heart's blood gave streptococci.
R 516	15–99	2 small doses; 1 very large	Last dose was 2 V.B.C.; died in 10 minutes; appeared in good health up to last injection	18 days	Small vegetation on free margin of tricuspid valve; hemorrhage into papillary muscle of mitral valve	Cultures from liver, spleen, and heart's blood gave streptococci.

In the table submitted only a few of the cultures obtained are represented. It is impossible to give in this space the details relating to so many different strains. Those given, however, have been carefully chosen so as to be as representative as possible and may be supplemented, if desired, by our records in the laboratory. Examples are described showing a gradation of lesions—from ordinary streptococci bacteremia without localization to endocarditis of the malignant, ulcerative type. Cases R 518, R 521, R 516, R 968, R 341 and R 665 are, in the order named, examples

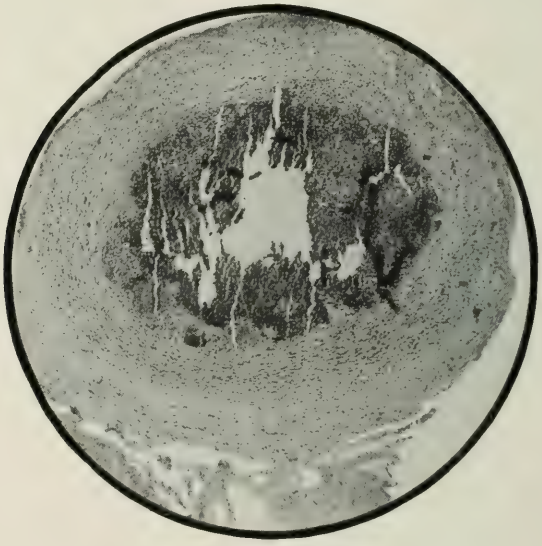

Fig. 6 (A 374).—Section of vegetation.

of just such a thing. Cases R 125 and R 281 are good examples of pericarditis in the absence of endocarditis. There seems to be, first of all, an affinity for the heart valves, and, failing this, the organism seems to pick out the pericardium, or, in a few instances, the myocardium. R 991 is a case illustrative of the latter. Of all the rabbits coming to autopsy, heart lesions were found in 56.6 per cent. Endocarditis was present in 40 per cent., pericarditis in 13.3 per cent., myocarditis in 6 per cent., aortitis in 3 per cent., while 30 per cent. gave a negative result. A slight degree of fever was present in all but one of the cases in which the temperature was taken. The

average temperature of the rabbits with endocarditis was 103.8°, the temperature of normal rabbits being about 102.5.° These figures refer to readings per rectum. One case had a subnormal temperature, 100.8°. Blood cultures were taken during life in a number of cases, but although the results are interesting they are necessarily inconclusive, since the measure was not carried out as a routine. It would seem, however, that, excepting in the later stages of the disease, it is fairly difficult to produce a constant bacteremia with the organisms under discussion.

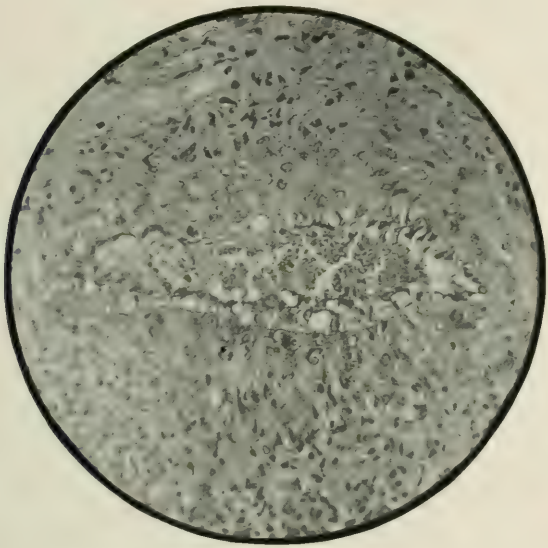

FIG. 7 (R 374).—Reaction about bloodvessel just beneath endocardium, which was bulging at this point. Probably early stage of mural vegetation.

With this data before us we feel that we have successfully demonstrated that while the organisms recovered in clinical cases of chronic infections of endocarditis are of an exceedingly low grade of virulence, they are nevertheless capable of producing in the rabbit not only a condition closely resembling that of the patient from which they were obtained, but also a condition which often ends fatally, accompanied by the usual signs of acute ulcerative, or so-called malignant endocarditis. We are therefore inclined to believe

with Rosenow[1] that the ordinary Streptococcus viridans or "endocarditis coccus" may produce all grades of endocarditis, and every grade may be produced in animals by the different strains of the organism. We also have shown that every grade of endocarditis may be produced in *different* animals by the *same* strain of organism.

Some evidence is at hand supporting the theory of implantation. A rabbit, R 374, inoculated with strain R 15–131 presented at autopsy a verrucose vegetation on the free edge of the valve. The microscopic examination of this specimen reveals no signs of capillary connection with this vegetation, and gives every appearance of its being merely an implantation upon the edge of a valve which has

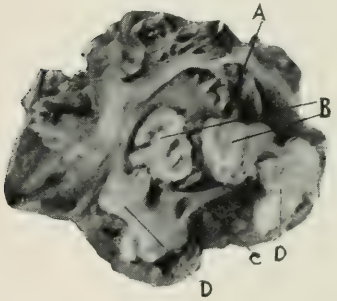

FIG. 8 (R 341).—*A*, right auricle; *B*, vegetations on tricuspid valves; *C*, right ventricle; *D*, *D*, cut surfaces of same vegetation.

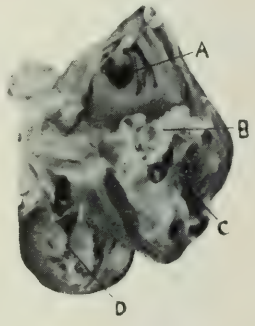

FIG. 9 (R 665).—*A*, right auricle; *B*, vegetations on valve cusps; *C*, right ventricle; *D*, left ventricle.

been subjected to the constant erosive action of the intimate but intermittent pressure of its fellow. The fact that in the same rabbit there is found a similar vegetation at the base of the valve, or on the valve ring, does not necessarily disprove or even cast doubt upon the implantation theory, especially in view of the fact that the site of the vegetation is on the auricular side of the valve. What does seem to favor the embolic theory, however, is the finding of hemorrhages in the valve curtains and under the mural endothelium, as the earliest evidence of the work of the bacteria, or bacterial emboli. Cultures of streptococci can be obtained from

[1] Experimental Endocarditis, Journal of Infectious Diseases, September, 1912.

these areas, and it is quite likely that on this favorable medium they begin the process which results in the familiar vegetation.

The clinical picture of the rabbit with chronic endocarditis resembles in a striking manner that of the patient with the same condition. The low grade of fever seems to be a constant feature of the disease, with periods of no fever, and bacteria-free blood stream. The fact that patients known to have endocarditis do not constantly yield positive blood cultures is, of course, well recognized. In the light of our findings there is no doubt in our minds that if only we had a way of knowing the opportune time, we might recover the streptococcus from the blood of many of these cases which now yield negative results. There is every reason to believe that the presence of streptococci in the blood does not necessarily mean, as was formerly supposed, a fatal issue. Rabbits from which we obtained positive blood cultures apparently in some cases recovered, lived for months and when chloroformed yielded negative results at autopsy. Similarly, clinical cases with bacteremia have improved and no doubt will entirely recover. The loss in weight of the rabbits with endocarditis was another noticeable feature of the clinical picture, which also corresponds with the findings in the human types. In some cases the emaciation was quite marked and, at least to some degree, seems to be a constant feature in the animals.

It is exceedingly interesting to note the evident elective localization upon the heart, and especially upon the heart valve, of these strains of streptococci, whose habitat was the heart valve and blood stream of their human host. Injected into the vein, they are pumped immediately into all parts of the body. Why do they not localize in the kidney, the appendix or the joints? Case R 281 was inoculated with a culture from the pericardial cavity of R 9780 S. with pericarditis. The autopsy next day revealed marked hemorrhages into the pericardium, and the pericardial surface of the heart was definitely inflamed. Yet the heart valves were perfectly normal. Surely there is something uncanny about the way in which these interesting organisms select their own peculiar scene of activity. Possibly much lies hidden in the expressions "elective localization" and "affinity" with which we dismiss these interesting phenomena from our discussions.

TABLE III

No. of rabbit.	Strain of organism.	Number and amount of intravenous injection.	Clinical picture.	Death after first inoculation.	Postmortem findings.	Postmortem cultures.
R 564	S. from a normal throat	4 injections of 6 V.B.C.	Temperature after first dose rose to 105.6° F.	16 days	Heart: Heart muscle pale in color. Tricuspid valve shows large vegetation, involving the whole valve curtain and forming adhesions with the cusp on the opposite side which is hemorrhagic and edematous; aortic valve almost completely stenosed, with vegetations on the valve cusps; mitral valve has a couple of small vegetations on the free margin	Cultures of the heart's blood and liver yield Streptococcus viridans.
R 562	P. from a normal throat	2 injections of 1½ V.B.C.	Temperature after first dose rose to 104.2° F.	3 days. Died a few minutes after last dose	Heart: Two small white vegetations on the tricuspid valve close to the free margin, also hemorrhage into one of the valve curtains about 3 mm. x ½ mm; large number of atheromatous patches in the aorta	No cultures taken, as the animal died so soon afte the last injection.
R 664	F.A. from a normal throat	2 V.B.C.	Three days later very sick; lies on its belly with all four legs extended, continually nodding its head; temperature 97° F.	Three days after inoculation; chloroformed	Heart: pericarditis, myocarditis; vegetations on the tricuspid valve, tip of the papillary muscle, and on the wall of the right auricle; these show a hemorrhagic area around them; one small vegetation also on the pulmonary artery 3 mm. above the valves	Culture from the blood shows streptococci; culture from pericardial cavity sterile.
R 576	M. from a normal throat	2 V.B.C.; 2 days apart	Five days after last dose rabbit very weak; Diastolic and systolic murmur could be heard over the heart; rhythm of heart irregular; died a few minutes after examination	Died 7 days after first inoculation	Heart: myocarditis; two small vegetations on the tricuspid valve, one above the other, and joined by fibrous adhesions; some small vegetations on the wall of the right ventricle; a big mass of verrucose vegetations almost completely blocking the orifice of the mitral valve and extending down to the papillary muscles	Cultures from heart's blood gave streptococci; also cultures from spleen and liver show streptococci.

TABLE III (Continued)

No. of rabbit.	Strain of organism.	Number and amount of intravenous injection.	Clinical picture.	Death after first inoculation.	Postmortem findings.	Postmortem culture.
R 568 (1)	McL. from a normal throat	Two injections: 1½ V.B.C.	After first injection temperature rose to 104.2° F. and rabbit developed a wry-neck	3 days	Kidneys: Show numerus focal pale areas scattered through the cortex. Heart: marked myocarditis, one small vegetation about the size of the head of a pin attached to the base of the tricuspid valve; two other vegetations at the bases of the papillary muscles; two vegetations on the mitral valve, one on each cusp and opposite to each other; atheroma of the aorta	Cultures from heart's blood and liver gave Streptococcus viridans; pericardium sterile.
R 573 (1)	Peq. from a normal throat	Three injections: 2½ V.B.C.	After first injection; temperature 106° F.	7 days	Heart: Myocarditis present; one large verrucose vegetation of the tricuspid valve, involving all the cusps and extending down onto the wall of the heart: one small vegetation on one of the cusps of the aortic valve	Cultures from heart's blood and liver gave Streptococcus viridans.

The similarity between the organisms recovered from the blood and the streptococci usually found in the tonsils and mouth of normal individuals is worthy of note. Not only is this to be noted in the sugar reactions but also in animal experiments. Nor is this similarity at all surprising. If we believe, as we claim, that the Streptococcus viridans passes through the diseased tonsil, suppurating alveolar socket, or other favorable lesions of the buccal and pharyngeal cavities, and entering the blood stream localizes upon the heart valves, is it to be wondered at that the similarity to the saprophytic relative still living in the mouth should be at least outstanding enough to be noticeable? We felt that it was altogether likely that these saprophytic streptococci living in the normal mouth could be proved to have the power to produce endocarditis in an identical manner to that of the organisms described in the

foregoing experiments and we inaugurated plans to carry on at once the necessary experiments to demonstrate this to be true.

Both Horder[1] and Rosenow[2] have reported the successful production of endocarditis in rabbits from streptococci isolated from normal saline (Horder) and tonsils (Rosenow). Their experiments, however, were very limited, and no attempt was made to issue accurate statistics. Our series, while larger, is not as comprehensive as we would have liked. Still, as far as it goes it is quite conclusive. The cultures for this series of experiments were obtained from the teeth, gums and tonsils of medical students in the bacteriological class-room. Eleven strains in all were used, and 31 rabbits were inoculated. The technic followed was identical with that used in the experiments recorded in the earlier part of this paper. All the strains were of the viridans variety of streptococcus. That is to say, they were capable of producing green on blood agar, gave typical fermentive reactions on the various sugars, and their other cultural characteristics were typical. They did not ferment inulin. Heart lesions of one kind or another were present in 80.6 per cent. of the rabbits. Of these myocarditis came first with 67.7 per cent., and endocarditis next, with 58 per cent. Aortitis was present in 32 per cent., and pericarditis was found in 22.5 per cent. Arthritis was demonstrated in 12.5 per cent.

Discussion. It will be seen that the percentage of positive results in connection with the mouth and throat series is greater than that of the series from strains recovered from the blood. This may be accounted for by the fact that some of the latter were subcultured several times before the first inoculation was made, whereas in the former, owing to increased facilities, we were able to begin inoculations from the first and second subculture, or as soon as a pure culture was obtained. This discrepancy was true only in a few cases, however, and the presumption is that the organisms, after reaching the blood, remain as avirulent as those which are left in the mouth.

The proportion of myocarditis is high, and evidently no higher than it should be. Although cloudy swelling and fatty degeneration

[1] Quarterly Journal of Medicine, April, 1909; Local Government Reports, 1906–7.
[2] Journal of Infectious Diseases, September, 1912.

were counted as myocarditis, the great majority had also focal areas of infiltration with round cells, and less frequently with polymorphonuclear cells. There were a great number of sections made in those cases showing upon casual examination no focal lesions, and careful study given them. It seems likely, from our findings, that the presence of these focal areas would be demonstrated in some hitherto considered negative.

The fact that none of the strains isolated from the blood in cases of endocarditis produced joint lesions, whereas definite arthritis was present in four cases from strains isolated from the mouth and tonsils, seems significant to us. Does it not strongly suggest two possible explanations: (1) that an organism may have in some instances a dual affinity, and depending upon environment and conditions existing in the particular individual in which they are present, they may attack one organ, or another, or both; (2) and more likely, that two types were present in one culture and each type produced its respective lesion? Pure cultures only of Streptococcus viridans were sought, and on being obtained, no attempt was made to grow the organism from one colony alone. When we speak of dual affinity, the term must of course be taken in its broad application. We all know that practically every pathogenic organism can attack a variety of structures. That is not what is meant, but just as the pneumococcus has a special predilection for the respiratory tract, though it does produce lesions elsewhere, and in the same way the meningococcus for the meninges, so the Streptococcus viridans confines itself to the heart, or again to the joints, or as we suggested above, to both. It seems plain from our findings at any rate, that the type of strain in the mouth and throat has a great deal to do with the type of lesion the patient is liable to develop. Take, for example, the results in respect to aortitis. The regularity with which this condition, in conjunction with endocarditis, was produced by certain strains is very striking. Strains L–7 and M–8 yielded aortitis in every instance. Strain M–8 was inoculated into six rabbits and definite aortitis resulted in all.

Although the Streptococcus viridans usually produces chronic lesions, in which round cells greatly predominate, it can attract leukocytes in relatively large numbers and therefore produce

microscopic abscesses. Sections of vegetations show a small area in the center composed chiefly of polymorphonuclear leukocytes with some of the nuclei undergoing fragmentation. There are also present some lymphocytes. Surrounding this focal mass of cells there is an area of proliferating endothelial cells. Some of the older vegetations show fatty changes with calcareous deposits in the center.

The focal areas in the heart muscle generally surround a small bloodvessel which is completely occluded by a bacterial embolus. There is a necrosis of the muscle fibers, and a round-celled infiltration composed of both polymorphonuclear leukocytes and lymphocytes.

In conclusion, let me venture to suggest that we have established three important points:

1. The Streptococcus viridans, isolated from the blood of cases of chronic infectious endocarditis, are of very low virulence, probably lower than any hitherto reported as being recovered from a similar source.

2. These streptococci are capable of producing in animals lesions identical to those found in the patients from whose blood the organisms were obtained.

3. The strains of Streptococcus viridans isolated from the mouth of normal individuals are similar to those isolated from the blood of patients suffering from chronic endocarditis, and are equally capable of producing heart lesions in the rabbit.

ON THE EXPECTORANT ACTION OF AMMONIUM CHLORIDE

By WARREN COLEMAN, M.D.
NEW YORK

Ammonium chloride is used so extensively in the treatment of respiratory affections that it is important to determine whether it does or does not possess an expectorant action.

All of the text-books on pharmacology which I have consulted regard ammonium chloride as an expectorant. Cushny, however, merely says that "ammonium chloride is generally credited with acting on the secretion of the bronchial mucous membrane, which it is said to render more fluid and less tenacious, and at the same time to increase considerably." The majority of text-books on therapeutics recommend ammonium chloride in the treatment of respiratory diseases.

In the discussion of Dr. Miller's[1] paper on "The Clinical Value of Expectorants," read before the Association of American Physicians, Dr. Meltzer said: "Ammonium chloride is, I believe, a reliable remedy for increasing secretion and expectoration." Other speakers expressed themselves in similar vein.

Yet on the basis of a few experiments upon lower animals in which important factors were not controlled, it has been denied that ammonium chloride, in the usual therapeutic doses, acts as an expectorant upon patients suffering from bronchitis.

In view of the doubt which has thus been created, I decided to reinvestigate the action of ammonium chloride upon the bronchial secretion in man. Patients with acute or chronic bronchitis were selected as subjects for the experiment. The objections which

[1] Tr. Assn. Amer. Phys., 1914, xxix, 139.

have been brought against the validity of such experiments do not appear to me to be fundamental. They are based upon the assumption that to act as an expectorant a drug must increase the total quantity of secretion within arbitrarily fixed periods. The generally accepted definition of an expectorant is a drug which facilitates the expulsion of mucus from the respiratory passages. Under this definition a drug may soften and release mucus from the walls of the bronchi without increasing the quantity in twenty-four hours. In fact, if we assume a healing effect of the drug upon the inflamed mucous membrane, as is generally done, the amount of secretion for the twenty-four hours may at times be actually diminished. Yet this does not invalidate the conclusion that the drug is an expectorant in the sense that it makes expectoration easier.

Experiments on Laboratory Animals. The experiments on the action of ammonium chloride upon the bronchial secretion of laboratory animals may be summarized as follows:

They were carried out on dogs and cats. The preliminary operations were done under chloroform or ether, or both. The trachea was severed in all experiments, in most of them the mucous membrane was exposed for direct observation. The anesthesia was prolonged by chloral, chloretone, or urethane.

The conclusions concerning the expectorant action of the drugs studied (ammonium chloride, ammonium carbonate, antimony, squill, senega, apomorphine, ipecacuanha, and pilocarpine) were based either upon inspection of the mucous membrane, or the weight of a piece of filter paper before and after it had been placed in contact with the mucous membrane, or by the amount of secretion which could be led off from the trachea through a tube. When there was no visible increase in the secretion and no increase in the weight of the filter paper, the conclusion was drawn that the drug under investigation did not possess expectorant properties.

All of these experiments are open to objections which vitiate the conclusions drawn from them. The objections are as follows:

No proof is offered that the anesthetics employed (chloral, chloretone, urethane) were without influence upon the bronchial secretion.

The evaporation of water from the exposed mucous membrane of the trachea is left entirely out of consideration. The control of this factor is of the highest importance.

The assumption is made that all expectorants produce a visible increase in the bronchial secretion under the conditions of the experiments.

Until these objections have been met the negative results obtained cannot be considered as conclusive.

One of the arguments advanced to disprove the expectorant action of ammonium chloride is that a large proportion of the drug is converted to urea in the liver—according to Biedl and Winterberg,[1] from one-half to four-fifths—and that with the usual therapeutic doses the amount reaching the general circulation would be too small to affect the viscosity of the bronchial secretion.

More recent experiments, however, do not support the observations of Biedl and Winterberg. Wolf and Osterberg[2] studied the influence of ammonium chloride upon the ammonia nitrogen curve in the urine. The experiment was performed upon one of the authors. The normal ammonia nitrogen excretion was first determined, and then 5 grams of ammonium chloride was taken in one dose. The result was as follows:

Average normal output of ammonia nitrogen = 0.366 gm.	0.732 gm.
Ammonia nitrogen in two days after ammonium chloride =	1.537 "
Difference	0.805 "
Nitrogen in 5 gms. ammonium chloride	1.308 "

This experiment shows that 52.5 per cent. of the ammonium chloride was eliminated by the kidneys alone in two days. Of special interest is the fact that the ammonia nitrogen curve in the urine reached its highest point within two hours after the ammonium chloride was taken. The urea excretion (expressed in terms of percentage of total nitrogen) fell from the daily normal of 79.50 per cent. to 75.40 per cent. on the day the ammonium chloride was taken. The ammonia nitrogen in the urine rose from 4.10 per cent. to 10.24 per cent. on the same day.

These results, together with the progressive increase in the

[1] Arch. f. d. ges. Physiol., 1901–02, lxxxviii, 140.
[2] Biochem. Ztschr., 1912, xl, 193, 234.

ammonia nitrogen content of the sputum, make it clear that in man little if any ammonium chloride is changed to urea in the liver.

The Plan of Experiment. The plan of experiment which I followed was: (1) examination of the sputum of patients suffering from acute or chronic bronchitis for the ammonia nitrogen content, and (2) observations upon the subjective symptoms referable to the respiratory passages following the administration of ammonium chloride.

If it can be proved that ammonium chloride is excreted as such, in appreciable quantities, by the bronchial mucous membrane, and if at the same time the secretion is more easily expelled, I believe that the expectorant action of the drug will thereby be established.

Seven persons, including Dr. B. F. Weems, house physician, a nurse in training, and myself were used as subjects of the experiment. All were suffering from acute or chronic bronchitis.

The sputum was collected before the administration of the ammonium chloride was begun and at various times thereafter. It was put at once into bottles containing chloroform and placed in an ice-box to prevent decomposition.

Subjective observations were made only by Dr. Weems and myself.

The doses of ammonium chloride varied from ½ grain every two hours to 5 grains every two hours.

The Ammonia Nitrogen in the Sputum.[1] Standard solutions were prepared containing 0.01, 0.02, 0.025, 0.03, 0.035, 0.04, 0.045, 0.05, 0.06, 0.07, 0.08, 0.09, and 0.1 mgm. of ammonia nitrogen in 5 c.c.

A sample of sputum from each patient was centrifuged and 1 c.c. of clear fluid was measured into a test-tube; this was diluted to 5 c.c. with water, treated with 10 drops of Nessler's reagent, and compared with the above standards (treated with an equal amount of Nessler's solution).

Typical results follow:

N. W. A. The ammonium chloride was taken in ½-grain doses every two hours.

[1] I wish to express my appreciation of the kidness of Dr. Stanley Benedict in making the chemical tests.

Before taking	0.02
After 10 grains	0.015
" 30 "	0.035
" 85 "	0.05

Davey. The ammonium chloride was taken in 5-grain doses every two hours.

Before taking	0.03
After 15 grains	0.025
" 60 "	0.06

Roselle. The ammonium chloride was taken in 5-grain doses every two hours.

Before taking	0.02
After 15 grains	0.03
" 60 "	0.095

There was a marked contrast in the ammonia nitrogen reactions of the saliva and the sputum. The reaction of the saliva was always faint, even under full dosage of ammonium chloride and when the intensity of the reaction of the sputum was progressively increasing.

Subjective Observations. Dr. Weems. Mild bronchitis of only several days' duration. Treatment begun on the second day of the attack with $\frac{1}{2}$-grain doses of ammonium chloride at two-hour intervals. Distinct loosening of the sputum and diminished roughness of the tracheal and bronchial mucous membrane followed. The taste of ammonium chloride was evident in the sputum at first; later the sense of taste for all substances was blunted.

Self-observations. Severe bronchitis of several weeks' duration. Treatment was begun at once but was suspended from time to time, and resumed for the purpose of repeating the experiment. The ammonium chloride was taken at first in $\frac{1}{2}$-grain doses every two hours and later in doses of 5 grains at the same intervals.

Whenever the drug was stopped the sputum became less abundant, more tenacious, and more difficult to expel, and a sensation of dryness or tightness developed in the chest. When the drug was resumed, the opposite effects were observed. The action of the drug always developed within one-half to one hour. The experiment was repeated too often to permit of doubt as to the accuracy of the observations.

Another fact of special importance was noted. For twelve or thirteen hours after a dose of ½ grain (the drug having been taken at two-hour intervals during the previous twelve hours) the taste of ammonium chloride, which is unmistakable, was evident in the sputum as it passed through the mouth. This observation possesses double significance—it identifies the form in which ammonium chloride is excreted by the bronchi (which was not established by the chemical analysis), and it demonstrates that the excretion of ammonium chloride is relatively slow in man—that is, in ½-grain doses every two hours it is ingested more rapidly than it is eliminated by all channels through which it leaves the body. The rate of excretion bears upon the question of the supposed transformation of ammonium chloride to urea by the liver, which has been referred to.

Mode of Action. The mode of action which appears most plausible is that ammonium chloride, during or after its excretion or both, lessens the viscosity of the mucus, partly through increasing the water of secretion and partly through solvent action, and that then the normal mechanisms of removal come more readily into play. Being less viscid the mucus is carried by ciliary action more rapidly toward the upper respiratory passages and finally is expelled from them by the act of coughing.

One of the experiments of Henderson and Taylor[1] may be interpreted as corroborating this view, though they cited it to disprove the expectorant action of ammonium chloride.

According to their protocol they exposed the mucous membrane of the trachea of a dog to view and measured the rate at which charcoal traveled through ciliary action. They found that human saliva could travel at the same rate, but that the actual rate depended upon the thickness of the layer. Weak solutions of ammonium chloride and ammonium carbonate, directly applied, did not increase the rate of the saliva beyond that of the charcoal. The addition of water increased the rate to a maximum as effectively as did the ammonium salts. They concluded that the viscosity of the saliva was of more importance than the salts in solution.

[1] Jour. Pharm. and Exp. Therap., 1910, xi, 153.

If it be assumed that ammonium chloride, in its passage through the bronchial wall, increases the water of secretion, the contention in favor of the expectorant action of the drug receives strong support from this experiment. According to this experiment, ammonium chloride does not increase ciliary motion. The experiment also removes the necessity of seeking an explanation for the expectorant action of the drug in stimulation of the bronchial gland centers or in stimulation of peristalsis in the bronchioles.

Summary. Clinicians generally believe that ammonium chloride is an expectorant. This action has been denied, however, on the basis of experiments on laboratory animals in which important factors were not controlled.

The action of the drug has been reinvestigated on patients suffering from acute and chronic bronchitis. The objections which have been raised to such experiments are not fundamental.

The excretion of ammonium chloride, as such, in the bronchial secretions has been proved.

Subjective observations have shown that ammonium chloride facilitates expectoration.

On the ground of these facts it is claimed that ammonium chloride is an expectorant within the definition of the term. It probably acts by increasing the water of secretions and softening the mucus.

DISCUSSION

Dr. Joseph Erlanger, St. Louis, said one could not be positive that the ammonium chloride found in the sputum was excreted by way of the bronchial mucous membrane. What precautions were taken to see that none of the ammonium chloride administered was retained in the mouth? Was any ammonium chloride eliminated in the saliva?

Dr. L. G. Rowntree, Minneapolis, asked at what stage in acute bronchitis does Dr. Coleman believe ammonium chloride is indicated? Is its action central or peripheral?

Dr. A. Jacobi, New York, said that some years ago, as many years ago as 1857, in lecturing before the students at the College of Physicians and

Surgeons, he had told them that ammonium chloride did not have the expectorant value of the carbonate or the acetate. Indeed, when he was a young man in Germany, it was the habit to give ammonium chloride as a placebo. Since then he had come to the conclusion that there is one indication for it: it will do something in chronic bronchitis where the sputum is sticky and hard to raise; it does seem to do some good in this condition.

Dr. Max Einhorn, New York, said he was delighted that the experiments were on humans rather than on rabbits. Animal experiments are good, but clinical work on patients is best, and personal observations of the effects of drugs on the experimenter himself are particularly valuable.

Dr. S. J. Meltzer, New York, said it seemed to him that Dr. Coleman's interesting experiments do not decide the questions concerning the expectorant action of ammonium chloride. As Dr. Coleman indicated, there are two kinds of expectorant: one increases secretion and the other increases the irritability of the mucous membranes of the bronchial tree, causes cough and thus helps the removal of the undesirable mucus.

The observation that a given substance is absent from a secretion is not evidence that the substance had no effect on the secretion; it may have done something while circulating through the blood of the corresponding mucosa.

Physicians should not give up something which good, critical clinical observers found useful—merely on the basis of complicated experimental evidence. His observation for many years has been that ammonium chloride is a useful expectorant. It will not save a patient destined to die, but it is a good palliative remedy.

Dr. Warren Coleman, New York, said his remarks had been confined to ammonium chloride; he hoped in the future to make further studies with other drugs. He replied to Dr. Erlanger that careful examinations of both sputum and saliva had been made by Benedict; only a very slight ammonia reaction was found in the saliva; the taste of ammonium chloride was present only in the sputum. As to the stage of bronchitis in which ammonium chloride is indicated, benefit may be expected after the first few doses in the early dry stage, as well as in later stages. The effect of the drug is probably due to its elimination by the bronchial mucosa, the water carried with it softening the secretion.

ALIMENTARY HYPERGLYCEMIA AND GLUCOSURIA AS A TEST OF SUGAR TOLERANCE

By LOUIS HAMMAN, M.D.
AND
I. I. HIRSCHMAN, M.D.
BALTIMORE

Jacobsen, in 1913, published an interesting study of the effects of different foodstuffs upon the blood-sugar. The food was given from two to three hours after a light breakfast and the blood-sugar estimated by Bang's micromethod at short intervals thereafter. He found that protein and fat had no influence upon the blood-sugar, but that carbohydrate produces a rapid and often a marked hyperglycemia. Following the administration of 100 gms. of glucose the blood-sugar, according to Jacobsen, rises rapidly, often going to 0.16 per cent. and higher, and then falls more gradually to the original level or in some instances even to a lower level; the whole reaction lasting from one to three hours.

A perusal of Jacobsen's results suggested the use of a similar method to study carbohydrate tolerance. Perhaps the character of the curve might be altered in different diseases and the test therefore yield important clinical data. In spite of the complex mechanism of carbohydrate metabolism, and our scant knowledge of the part played by the different factors concerned in the storage, mobilization and utilization of sugar, the simple estimation of a patient's ability to promptly dispose of a certain amount of glucose taken at one time into the stomach, or as usually named, his glucose tolerance, has definite clinical value. The method generally employed for this purpose is to feed patients glucose in increasing amounts until sugar appears in the urine. There are difficulties

and inconveniences in the way of carrying on such an investigation. It is rarely possible to hit upon the proper amount of glucose at the first dose, and therefore the test must be repeated a number of times. Solutions of glucose above 100 grams make a nauseous draught for most patients; not infrequently they vomit the mixture and the test must be abandoned. Besides these difficulties there are also sources of error in the method because no account is taken of the renal threshold for glucose. Sometimes otherwise normal persons have a low renal threshold and sugar appears in the urine, although the blood-sugar is only a little raised; more commonly still the renal threshold is high, and little sugar or none comes out in the urine, although the blood-sugar mounts to a high level. Under such circumstances one would conclude erroneously, in the first instance, that the patient had a low sugar tolerance; in the second instance, a high sugar tolerance. It would be a decided advantage could we give a single and a constant dose of glucose, and from a study of the patient's reaction satisfactorily determine the sugar tolerance. We believe that the method we have employed furnishes us this information in an altogether satisfactory way and that it adds besides an insight into the carbohydrate economy that the rougher tolerance test does not give.

Method. The patient to be tested receives 100 grams of glucose in a lemonade in the morning after the night fast. The blood-sugar is determined before the glucose is given and thereafter at frequent intervals. Specimens of urine are collected immediately before or immediately after each blood specimen is taken; or if the patient is unable to void so frequently, as often as they can be obtained. The urine is carefully examined for sugar and if sufficient is present the quantity determined separately in each specimen. We have found it advisable to prepare the lemonade by dissolving the glucose in warm water, adding the juice of several lemons, or of two lemons and an orange, making the mixture up to 300 c.c. and cooling by packing in ice. Such a mixture is not disagreeable to take, and rarely causes nausea. If larger quantities of water are used patients often complain of the bulk, and sometimes of nausea after drinking it. In our studies we have made from five to nine blood-sugar determinations in from two to three hours. The blood is obtained

by puncture of an arm vein at the bend of the elbow, a little over 2 c.c. of blood being withdrawn at each puncture. It may seem a formidable procedure to undertake so many venapunctures at such short intervals, but in fact it is neither difficult for the operator nor disagreeable to the patient. If a vein has once been fairly entered, the needle may thereafter be passed in through the same puncture and the patient scarcely be aware of the operation. The only important warning is to avoid making suction until the needle is fairly in the vein, and to desist before the needle is withdrawn. A small hematoma may so obscure the location of the vein that another site must be selected for the next puncture. In fat subjects this is often a disadvantage. We are assured by patients who have had experience with both methods that repeated pricking of the ear or finger-tip is more disagreeable than an equal number of venipunctures skilfully performed. In these studies we have made more frequent blood-sugar determinations than are really necessary. We believe that four determinations, one before administering the glucose and the others a half-hour, one hour, and two hours after, will give all needed information. We have used the Lewis-Benedict blood-sugar method following the technic originally described. Numerous control estimations upon glucose solutions of known strength have convinced us of the remarkable accuracy of the method. Heating the mixture in a test-tube over a free flame is tedious and time-consuming, but we have been unable to get accurate results in other ways, and we have tried heating in beakers over a steam-bath, and in the autoclave at different pressures. In examining the urine Benedict's qualitative and quantitative methods were employed.

Reactions in Normal Persons. Jacobsen's studies on alimentary hyperglycemia following the administration of glucose were made upon fourteen so-called normal persons. The blood-sugar rose to from 0.12 per cent. to 0.23 per cent. The rise occurred rapidly, the highest point being reached in from fifteen minutes to one hour; the fall is more gradual, the reaction occupying from forty-five minutes to three and a half hours. Most of the persons tested by Jacobsen had a single urine examination, but some had two and a few three. The six whose blood-sugar did not

rise above 0.16 per cent. had no sugar in the urine; the eight whose blood-sugar went above 0.17 per cent. did have glucosuria.

We are unwilling to allow that Jacobsen's figures be accepted as the standard for normals. It is generally conceded that normal persons do not have sugar in the urine after the ingestion of 100 grams of glucose, even when the glucose is taken into a fasting stomach. Undoubtedly most of Jacobsen's subjects had a somewhat lowered carbohydrate tolerance. Our results, as well as those obtained by Hopkins, support this contention.

Hopkins has studied the effects of 100 grams of glucose upon eight normal persons. The blood-sugar rose to from 0.11 per cent. to 0.156 per cent.; the highest point was reached in from thirty minutes to two hours. In the six instances followed to the end of the reaction the reaction occupied from one and a half to three and a half hours. No urine examinations are reported.

In six normal persons the authors found that after 100 grams of glucose the blood-sugar rose to from 0.1 per cent. to 0.139 per cent.; the high point was reached in from twenty minutes to one and one-half hours; the whole reaction occupied from one to two hours. Although the blood-sugar of none of the six rose to 0.15 per cent., still two showed glucosuria. In one of these the blood-sugar went to 0.138 per cent., in the other to 0.124 per cent. We have established that the normal renal threshold for glucose is between 0.17 per cent. and 0.18 per cent. of blood concentration. Therefore these two patients have an unusually low renal threshold; perhaps one might speak of it as a potential renal diabetes.

Reactions in Diabetes. Jacobsen reports the effects of 50 grams of white bread upon the blood-sugar of five diabetics. Three of the cases were sugar-free when the test was begun; the other two had respectively 0.26 per cent. and 0.36 per cent. of sugar in the urine. Following the administration of 50 grams of bread, the equivalent of 27 grams of glucose, the blood-sugar rose rapidly but somewhat slower than in normals, the high point being reached in from one to one and a half hours; this high point was maintained for from thirty minutes to an hour, giving the curve a rounded instead of a sharp summit; the fall was then gradual, the whole reaction occupying from two to over three hours. In two of the

patients, sugar-free at the start, the blood-sugar did not reach 0.15 per cent., and still appreciable amounts of sugar appeared in the urine. Jacobsen comments upon this disproportion, stating that diabetics excrete more sugar at a given blood-sugar level than do normals. We have elsewhere pointed out that in diabetes the renal threshold is often abnormally low, and this low threshold is the cause of the difference Jacobsen has noticed.

Hopkins has studied the hyperglycemia following the administration of 100 grams of glucose to nine diabetics. All of these patients had a high blood-sugar and glucosuria when the test was given. Hopkins comments upon the pronounced hyperglycemia that follows, and the prolongation of the reaction as compared with normals.

We have studied twelve reactions upon ten diabetics, administering from 10 to 100 grams of glucose according to the severity of the disease. The severity of the disease was judged by the ease with which the patients were rendered sugar-free by fasting and their ability subsequently to utilize carbohydrate without the appearance of glucosuria. The cases are thus roughly divided into mild, moderately severe and severe diabetes.

The reaction following the ingestion of glucose by diabetics is very different from the reaction of normal persons. Our studies do not give strictly comparable data, for only three of the diabetics received 100 grams of glucose. However, these three patients, having but a mild derangement of carbohydrate metabolism, illustrate strikingly the essential change in the diabetic reaction as contrasted with the normal. All three had moderate glucosuria, excreting respectively 6.8 grams, 7 grams and 3 grams of sugar. The blood-sugar rises more slowly than in the normal, the highest point being reached after forty-five minutes, one hour and twenty minutes, and one hour and forty-five minutes; the blood-sugar rises to a much higher point than in the normal, all three exceeding 0.2 per cent.; the high point is maintained for nearly an hour in two instances, for only a short period in the third; the fall of the blood-sugar occurs much slower than in the normal, the whole reaction occupying from three to four hours. Two of the patients have a normal renal threshold; in the other the threshold cannot be

accurately fixed but is somewhere between 0.13 per cent. and 0.2 per cent.

These general features of the diabetic blood-sugar curve are faithfully reproduced by the other patients receiving, on account of the severity of their disease, smaller amounts of glucose. In some of the curves the blood-sugar is just beginning to drop three hours after taking the glucose. Apparently the duration of the reaction is a more important index of the alteration of carbohydrate metabolism than the height of the reaction. In some of the patients a definite diuresis accompanies the glucosuria and this tendency is particularly noticeable in the severe cases. The matter of the renal threshold is important, for no doubt variations in this factor are responsible, at least in part, for the impression that there is an entire lack of proportion between the degree of hyperglycemia and the accompanying glucosuria. The fact that heretofore comparisons have been made between the amount of sugar in the urine collected over a relatively long period of time and a single blood-sugar determination is a more important source of error. We have not yet studied our figures sufficiently closely to be able to state that there is a definite and constant relation between blood-sugar and urine sugar, but it is clear that, taking into account the renal threshold, there is at least a gross proportion between the two.

Reactions in Nephritis. It has long been known that in nephritis the blood-sugar is often unusually high. However, it is not always high; sometimes it is at the normal level; and why some cases have hyperglycemia and others have not has never been satisfactorily explained. Attempts to bring the hyperglycemia into relation with the blood-pressure have not been wholly successful. Hopkins reports a large number of single blood-sugar observations upon patients with nephritis, and in addition gives the results of an alimentary test upon four of the cases. Three of these show a marked hyperglycemia after 100 grams of glucose, two going above 0.2 per cent. The high point is fairly well sustained at least, the summit of the curve is rounded, and the fall is rather slow, the whole reaction occupying from three to four hours.

We have made observations upon six patients with nephritis. A patient with chronic diffuse nephritis and hypertension, bordering

upon uremia, gave a definite "diabetic type" of blood-sugar curve, but only a trace of sugar appeared in the urine, although the blood-sugar went to 0.2 per cent. The fasting blood-sugar was at the upper limit of normal. The renal impermeability explains the absence of glucosuria in spite of the marked hyperglycemia, but does not explain the profound disturbance of carbohydrate metabolism portrayed in the blood-sugar curve.

A patient with marked hypertension and only moderately impaired renal function gave a reaction altogether similar to the reaction of a mild diabetic. The fasting blood-sugar was high, 0.136 per cent.; the renal threshold was 0.17 per cent.; the blood-sugar amounted to 0.264 per cent.; the summit of the curve was rounded; the whole reaction occupied three hours; a large amount of sugar was excreted. Obviously in this instance renal impermeability played no part in producing the hyperglycemia.

Another patient with hypertension and only moderate impairment of renal function gave a similar though not so marked a reaction. The blood-sugar curve rose slowly, was rounded at the summit and fell slowly, but the highest point was at 0.174 per cent., and no sugar appeared in the urine.

In contrast with these three reactions is the reaction of a patient with chronic diffuse nephritis without hypertension. The blood-sugar curve was a little more prolonged than in the normal type but it did not show the striking "diabetic" features of the others.

Still another patient with chronic diffuse nephritis with hypertension and with almost normal renal function gave a still higher and more prolonged blood-sugar curve. The urine examinations were equivocal, since all of the specimens contained pentose.

These observations influenced us strongly to regard hypertension as an important indicator of disturbed carbohydrate metabolism and tempted us to seek the common explanation for both in altered adrenal function. However, a recent observation temporarily, at least, upsets this speculation. This observation was made upon a patient with chronic diffuse nephritis and hypertension with only moderately impaired renal function. Our first test made two hours after breakfast yielded a perfectly normal reaction. Hoping that the breakfast might have been accountable for this

unexpected result, the test was repeated. Again a practically normal curve was obtained. In the face of this evidence we cannot correlate hypertension and alimentary hyperglycemia.

Therefore in many cases of nephritis there is a profound change in carbohydrate metabolism, the blood-sugar curve after the ingestion of glucose resembling the "diabetic curve." When there is marked interference with renal function very small amounts of sugar or none appear in the urine, although the blood-sugar may go above 0.2 per cent.

Reactions in Disturbance of Thyroid and Hypophyseal Functions. Excepting disease of the pancreas, disturbance of thyroid function is the commonest cause of altered carbohydrate tolerance. The clinical manifestations of thyroid disease are notoriously variable, and the grouping of the different symptoms occurs in a confusing way. Vagotonic and sympathicotonic symptoms are often hopelessly mixed, and in one patient evidence of overfunction and underfunction may occur side by side. Sugar tolerance shows the same perplexing combinations. However, in a general way in hyperthyroidism it is low; in hypothyroidism abnormally high, although individual patients display wide latitude in their response. It has been known for a long time that hyperglycemia commonly occurs in Graves's disease, and recently the subject has been studied again in a thorough way by Geyelin.

Since Cushing has demonstrated the important part played by the hypophysis in the carbohydrate economy disturbance of hypophyseal function has come to rank second only to thyroid disease as a fertile source of altered sugar tolerance. In disorders of this gland, as in thyroid disease, hyperfunction is associated with decreased tolerance, hypofunction with an increase; but similar individual differences occur. Up to the present time observations of carbohydrate tolerance in thyroid and hypophyseal disease consist of urine examinations and of single or at most occasional blood-sugar estimations. While these observations have established important facts they give no insight into the underlying metabolic disturbance. Only Hopkins has studied the curve of alimentary hyperglycemia in two cases of hypophyseal disease. In both instances there was an abnormally high and prolonged reaction.

We have made observations upon six patients with thyroid disease and five with hypophyseal disorders.

The five patients with obvious hyperthyroidism show a lowered sugar tolerance. The blood-sugar curve has to some extent the high, sustained, prolonged features of the diabetic type. All five had glucosuria, but only one put out a large amount of sugar. One patient had but a slight glucosuria, although the blood-sugar went above 0.2 per cent. The patient had albumin and a few hyaline casts in the urine, no doubt a mild nephritis with renal impermeability. The sugar tolerance is more seriously disturbed than a study of the urine alone would indicate. One patient is of special interest on account of the improved sugar tolerance one month after operation. A young man with a large colloid goitre and no obvious symptoms of disturbed thyroid function, gave a normal reaction.

Two patients with well-marked symptoms of overfunction of the hypophysis both yield typical "mild diabetic type" of blood-sugar curves. A mildly acromegalic in the quiescent or underfunction stage has an unusually low fasting blood-sugar and shows only a slight rise of blood-sugar after 100 grams of glucose, indicating a high sugar tolerance. Finally, the patients with only suggestive symptoms of deranged hypophyseal function gave, one a normal reaction save for the remarkable diuresis, the other the characteristic reaction of low glucose tolerance.

Reactions in Various Diseases. In concluding we wish to report the reactions in a few patients with various disorders. A patient with general paresis, convalescing from pneumonia, and a patient with asthma, showed a moderate decrease in carbohydrate tolerance; both excreted a little sugar after the administration of 100 grams of glucose. A patient sent into the hospital as a diabetic on account of occasional glucosuria, showed a rather high and definitely prolonged reaction without glucosuria. The test suggested only a little disturbance of sugar tolerance, and even on a very liberal general diet the patient never had glucosuria while in the hospital. A patient from the gynecological service was investigated also on account of transient glucosuria. Except for being somewhat high, the curve was otherwise normal, and subsequently sugar

was not again found. A patient with rheumatic fever was having afternoon elevation of temperature up to 101° at the time the test was done; he had only a very slight rise of blood-sugar after taking 100 grams of glucose.

Conclusions. 1. The study of alimentary hyperglycemia and glucosuria gives a valuable insight into the carbohydrate economy.

2. In a general way there are two types of reaction to the ingestion of glucose.

(*a*) The normal reaction in which there is a slight or moderate hyperglycemia that rapidly subsides.

(*b*) The diabetic reaction, in which the hyperglycemia is more pronounced and more prolonged.

3. The occurrence of glucosuria and its extent depends upon the degree of hyperglycemia and the renal permeability. The normal renal threshold is between 0.17 per cent. and 0.18 per cent. of blood-sugar concentration. In some normal persons, and commonly in diabetics the threshold is low. In many patients with nephritis, and frequently in diabetics the threshold is high.

4. As far as may be judged from the alimentary test, the disturbance of glucose utilization is essentially the same in diabetes and in other conditions with low sugar tolerance, such, for instance, as is commonly associated with deranged thyroid and hypophyseal function and with nephritis.

CLINICAL INVESTIGATIONS ON INTESTINAL AUTO-INTOXICATION, ESPECIALLY AS REGARDS THE QUESTION OF SPECIFICITY OF TOXIN

By THOMAS R. BROWN, M.D.
BALTIMORE, MARYLAND

We wish to present very briefly a few observations on the specificity of toxin or bacteria in certain cases of so-called intestinal toxemia or bacteriemia, not in an attempt to draw any definite conclusions from these observations, but rather to chronicle certain rather striking findings in the hope of stimulating discussion on this subject of so much interest and yet of such almost universal misconception. These cases, although few in number, were studied rather intensively in the hospital, where each was under careful observation for a period of at least four weeks; they comprised 3 cases of chronic eczema and urticaria, 1 of pruritus, 2 of so-called bilious headache, and 1 of choroiditis. The 3 cases of chronic extensive eczema with urticaria gave almost identical histories, the salient points of which were as follows:

Case I.—Young man, aged twenty-six years. Negative past history, except a little eczema all his life; hay fever every summer; an absolutely normal digestion before the present illness, except a slight tendency to constipation; rather nervous; moderate user of alcohol and tobacco. Present illness began nine months before he was seen by us—eczema of the big toe, gradually spreading until it now involves the whole body; has had many treatments, but all unsuccessful. The salient points of the physical examination were a very extensive eczema, scaly or weeping, with also some definite urticaria, a normal blood count, except 12 per cent. of the eosinophiles and 46 per cent. of neutrophiles; test meal: free hydrochloric 10, total 15; stool cultures aërobic normal, anaërobic sterile; test meal on leaving hospital, normal (six weeks later).

Case II.—Man, aged fifty-four years. Absolutely negative family and past history; onset of present illness five months before, beginning on thighs, and now involving entire body, associated with attacks of urticaria and angioneurotic edema. Physical examination showed a moderately enlarged liver, a diffuse papular, squamous eczema, with some urticaria, a normal blood count, the eosinophiles being but 2.5 per cent.; stool examination negative both as regards bacterial, chemical, and microscopic findings; test meal: free hydrochloric acid 18, total 30.

Case III.—Woman, aged forty years. Absolutely negative past history except tendency to constipation, with slight gastric indigestion. The patient had had a diffuse eczema with urticaria for over a year without definite cause. The physical examination showed this condition and was otherwise negative, except that the test meal showed a complete absence of free hydrochloric acid; the stool and the blood were normal.

Tests of cutaneous sensitiveness to proteins were made in all 3 cases by the method employed by Blackfan—milk, egg-white, horse serum, meat juice, and barley proteid being employed. The first 2 cases showed marked hypersensitiveness to all the proteins, except that there was no reaction to egg-white in the second case and very slight in the first. The third case showed no cutaneous reaction to any of the proteins. In the first 2 cases a meat-free diet with no cereals brought about a rapid improvement, leading to a permanent cure; in the third case the effects of such a diet were *nil.* In the first case, after two weeks of complete freedom from skin lesions, the giving of one egg reproduced within twenty-four hours the original cutaneous picture; but after another two weeks of meat-free diet, egg-white was given in teaspoonful doses daily, gradually increased, subsequently feeding other proteids in a similar way, so that now his tolerance has been so increased that he is able to take eggs, milk, and simple meats in moderate amount with no ill effects. He as well as the second patient has now been entirely well for nearly a year.

The case of pruritus was most interesting in many respects. The patient was a very nervous woman with a negative past history, except for several mild abdominal attacks suggestive of appendicitis, and also the history of chronic constipation. The physical examination showed marked cecal stasis, with slight tenderness on deep palpation, verified fluoroscopically as being due to a chronic appendi-

citis. The pruritus, which was general, followed directly upon an acute attack of indigestion, about eight months previous to her visit to us, which seemed to be referable to eating crabs and milk, and had continued ever since, although markedly aggravated by excitement and worry, and alleviated by the simple life. The gastric examination showed a true achylia, the stool cultures were negative, while her protein sensitization test showed a marked reaction with milk, but none with the other proteins employed. On a low protein diet, practically meat-free, with milk entirely eliminated, and the administration of hydrochloric acid and attention to the constipation, the pruritus gradually disappeared, and has now been absent for more than a year, while the study of her gastric contents shows a return of hydrochloric acid, though still distinctly subnormal.

The 2 cases of bilious headache had practically identical histories —chronic constipation associated with periodical attacks of severe headache associated with an increase in constipation, nausea and vomiting, and always relieved by free purgation, especially by calomel and salts. Each showed a complete absence of hydrochloric acid in the gastric contents, no hypersensitiveness to the protein substances employed, each was markedly relieved by a diet from which animal proteid food was practically eliminated, and in each an increase in the bowel sluggishness, a typical bilious headache, and, what was most interesting, a temporary but marked increase in the size of the liver could be brought about by giving meat for a short period of time.

The last case was perhaps the most interesting of all, for this was the only one of our series in which the bacteriological study of the stool gave pathological findings. This patient had recurring attacks of choroiditis, always preceded by digestive disturbances.

Case IV.—A young woman, aged twenty-seven years. Had typhoid fever at eighteen years, chronically constipated for about thirteen years, necessitating the constant use of purgatives, while the present illness was simply a continuation of her old history of constipation, although getting gradually worse, with weakness, gastric and intestinal indigestion, pain in the stomach and in the lower abdomen shortly after eating, not related to the menstrual function, with, for the past four years, attacks of eye-ache and recently distinct impairment of vision. The physical examination showed a marked visceroptosis, with a maximum degree of cecal stasis,

and fluoroscopic evidence of chronic appendicitis, a negative Wassermann reaction, a moderate anemia, practically normal gastric contents, the typical ophthalmoscopic picture of repeated attacks of choroiditis with old, black hemorrhagic deposits, while the stool examinations, of which twenty-six were made in conjunction with Dr. Sylvester, at the Woman's Hospital, showed when the stool was acid nothing especially characteristic except occasionally a very few anaërobes, while with an alkaline stool the predominating organism was a large diplococcus, anaërobic, Gram-negative, with quite a number of a large and a small Gram-negative anaërobic bacillus.

The striking features of this case were (1) the apparently definite connection between the acute intestinal disturbances and the "eye-aches" of the patient, ophthalmoscopically recognized as acute attacks of choroiditis; (2) the fact that with these attacks the stools were always alkaline, while bacteriologically there appeared as the predominant microbes three Gram-negative anaërobes which we were unable to definitely identify, notably a large diplococcus, these anaërobes usually being practically absent when the stool was acid, while the diplococcus was isolated in pure culture from the appendix at the time of an appendicostomy operation performed later; (3) the extreme difficulty in keeping the stool acid even with a meat-free carbohydrate-rich diet, and enormous doses of an acid-forming bacillus—the Bacillus bulgaricus; (4) the considerable improvement brought about by a low proteid diet, which was markedly increased by an appendicostomy with colonic irrigation through the new opening; (5) our ability to prophesy the choroidal attacks from the alkalinity of the stool and its large content in certain anaërobic bacteria.

When we speak of toxic symptoms we are unquestionably treading on debatable ground, and yet certain of the symptoms met with in these cases are explicable only on this basis. What is the cause of these toxic symptoms? Is it a toxin normally present or in excess? Has the protective mechanism become insufficient possibly due to repeated mild anaphylactic reactions, or is there a tendency toward an overgrowth of certain bacteria, notably proteolytic anaërobes, and may immunity be brought about in time? Whether these toxins are derivatives of the amino-acids we cannot say, but it is striking what slight changes in molecular constitution are necessary to convert the normal bases into products of great toxicity,

and it is certainly possible that this may be brought about by the proteolytic intestinal bacteria. The work of Eppinger and Guttman in isolating two ptomains from the stool, one producing urticaria, the other asthma, is extremely suggestive in this connection. Whether these toxic anaërobes are always present in minimal amount, or whether they originate from external sources, such as tainted meat or pyorrheal pockets, has not been determined. That the poisons, produced by these bacteria or due to other causes, cannot often be demonstrated is not so much a proof of their absence as of their extreme complexity, and of the minimal amounts in which they must be present in urine, blood, and stool. The mechanical and surgical conceptions of intestinal stasis are quite insufficient to explain the symptom-complex presented. Back of the mechanics of digestion lies a problem far more complicated, far more difficult to solve, the problem of congenital or acquired hypersensibility to certain stimuli, the question of the overproduction of certain toxic substances, their chemical nature, and their possible specificity, and various questions involving more definitely physical factors, notably absorption and osmosis.

In our series it is hard to escape the conclusion that in the intestine certain substances are produced which in some instances are possessed of specific action associated with a hypersensitiveness to certain proteins not in themselves toxic but possibly capable of producing a reaction because of an acquired hypersensibility, and that therapeutically a marked improvement in symptoms and even a complete cure may be brought about by the elimination of these substances from the dietary. It is also suggested by a study of these cases that by giving these foods in gradually increasing amounts a marked increase in resistance may be produced. That in certain cases at least the symptoms are better explained on the basis of a bacterial infection of intestinal origin rather than upon that of a toxemia, and that in various cutaneous lesions, testing the cutaneous sensibility by intradermal injection of various proteins is of real value in determining whether or not the condition may be due to certain toxic bases of intestinal origin derived from the decomposition of certain protein foods. These reactions are apparently specific in character, that is, are only seen to be present when the

toxins produced have a specific effect upon the skin, and therefore these tests of cutaneous hypersensiciveness to various proteins probably cannot be used as criteria of other conditions best interpreted as protein intoxications with manifestations elsewhere than in the skin.

OBSERVATIONS ON RHEUMATOID ARTHRITIS

By RALPH PEMBERTON, M.D.
PHILADELPHIA

It is the purpose of this paper to present in brief form the end-results to date in a study of about fifty cases of rheumatoid arthritis. It seems that there can be advanced a useful and additional method of treating this disease. This method is not at variance with the prevailing view as to the relation of foci of infection, but is supplementary to it, and is applicable in many cases where attempts at treatment along infectious lines fail of success.

There seems to be conclusive proof that the ingestion of carbohydrate and possibly protein food bears a very close and specific relation to the incidence and perpetuation of this disease. If it be assumed that all cases of rheumatoid arthritis are due to foci of infection, then it follows that the effect of such foci can often be negatived by dietary control. A dispassionate view of the situation is that foci of infection are often, though not always, the cause of rheumatoid arthritis, and should be removed where possible. Failing this, or if the symptoms persist after such removal, a restriction of diet in the manner to be mentioned will often give striking results. Even in the presence of foci of infection, provided they be not of a gross surgical nature, a restriction of diet may bring about improvement or cure.

The principle upon which this dietary control depends is that there seems to be in most cases of rheumatoid arthritis a level of intake of carbohydrate and possibly protein food, above which the symptoms persist and below which they tend to diminish or disappear. In regard to the three factors, carbohydrate, protein, and fat,

the exact role which each plays has not been determined, but the evidence is strong, as the result of experiments to this end, that the carbohydrates alone can induce and perpetuate the disease. Curtailment of this factor has afforded one basis of this method of treatment, and has yielded good results. Experiments, however, have also been made in which the disease has been reinduced, in cases rendered free from it, by the ingestion of pure carbohydrate. The symptoms have again subsided when the carbohydrate was withdrawn. Observations still pending on the proteins and fat will not allow at this date of such definite conclusions concerning them, but there is evidence that fat can be better tolerated than carbohydrate. It cannot yet be stated that fat can be tolerated with impunity, but it seems at present that it can be borne better than can carbohydrate. Fat is apparently not a direct factor in the causation of this disease. This is of theoretical interest, because it indicates further that one or both of the other factors are harmful, and it is of practical value in treating the disease, since the caloric total of the diet can be raised by fat in a relatively innoxious manner.

Of the protein elements, it can now merely be said that the removal of them from the diet is not in itself curative, unless in so doing the total food intake and caloric total be considerably reduced. Protein can apparently be borne in amounts in excess of the minimum requirements. A variety of experiments has been carried out to determine the *modus operandi* of these factors, but this is not yet clear. It is conceivable that the role played by the foodstuffs depends upon bacterial activity in the intestinal tract. If so, observations still incomplete suggest, subject to later modification, that it depends upon the substrate of food rather than upon the type of organisms *per se*.

Treatment depends upon the restriction of food intake to a point which varies with the individual case. This point cannot be accurately determined beforehand, and the writer has found it useful to approximate in calories the normal intake of food in a given case for upward of a week. From this approximation some hazard can be made as to how much reduction there must be in the new diet. In outlining this it is essential, of course, that the necessary nitrogen requirement as supplied, though it does not seem essential to limit

the protein as strictly as the carbohydrate. The remaining caloric total is then made up of a small amount of carbohydrate, varying say from 30 to 60 grams of bread a day, together with as large an amount of fat within the reduced caloric total as the individual can successfully digest. It is doubtful whether the full caloric total of the normal food intake can be made up by fat. A sample diet in a case of this disease, therefore, will consist of one or two eggs, 35 to 50 grams of meat, 2 or 3 slices of bread of 30 grams each, 30 to 40 grams of butter, and 50 to 100 c.c. of pure olive oil in the form of mayonnaise and French dressing on lettuce, or even taken straight. For the protracted periods during which the diet must be followed, it is important that the meals be made as apparently satisfying as possible, for which purpose green vegetables and thin soups can be given in addition.

No attempt has been made here to detail the laboratory findings, but it may be said that the carbon dioxide tension of the alveolar air shows no clear departure from normal, and that there is no evidence to indicate acidosis or any disturbance in elimination or in the blood nitrogen, during either ill health or convalescence. The writer[1] recently reported observations on the hydrogen ion concentration of the urine and offered the tentative conclusion that coincident with natural or induced exacerbations of this disease there was a tendency for the urine to show a decreased acidity. This has found some, though not invariable, support in later observations. The significance of this change is not now apparent, but it is pertinent to note that cartilage, a tissue largely affected in this disease, is very high in sodium.

No attempt is made here to state the exact proportion of cases which will respond. In one case out of thirty-eight no effect from diet could be appreciated, and space will not permit of discussing the response from the various types of the disease. There are limitations to treatment presented by general debility, emaciation, advanced cardiac disease, etc., and in such cases the individual may not be able to tolerate a restriction of diet, however slight. The more severe the disease and the greater its duration, the more

[1] American Journal of the Medical Sciences, March, 1916.

difficult it is in general to obtain results and the more restricted must the diet be; but there are well-marked exceptions to this. In every case it is important to consider first the general condition of the patient, and only when this is satisfactory can the methods in question be practised, if they entail severe dietary restriction.

To summarize, there is here advanced a definite method of therapy which will apparently arrest many cases of rheumatoid arthritis, will often prevent the establishment of the disease when the symptoms first appear, and seems also to throw light on its etiology and nature. It is not to be expected that every case will respond equally well. The secondary results of the disease are often harder to treat than the disease itself.

Arrest of the causative arthritis does not undo the structural harm done, and often, after it is not longer active, there are many factors productive of pain and disability. The principle which this article endeavors to point out is that rheumatoid arthritis is often referable to the dietary elements above indicated. The proof of this principle can be appreciated in a large majority of cases in which a restricted diet is applied and subsidence of the inflammatory process follows to a greater or less degree. This is independent of the question of complete restoration to health which is conditioned by various factors in which the chronicity of the disease and its sequelæ play an important role.

A STUDY OF THE GERMICIDAL ACTION OF QUININE AND UREA HYDROCHLORIDE, OPTOCHIN, AND OTHER CINCHONA DERIVATIVES UPON PNEUMOCOCCUS CULTURES IN VITRO*

By SOLOMON SOLIS COHEN, M.D.

AND

JOHN A. KOLMER, M.D.

PHILADELPHIA

(Abstract)

A LONG-CONTEMPLATED research upon the true value and method of action of quinine compounds in the treatment of pneumococcus infections, and especially of lobar pneumonia, was made possible by the generosity of a patient, Mr. Samuel Fels, of Philadelphia.

The clinical methods followed for many years, the results obtained and the opinions formed by one of us (S. S. C.), and his desire that these be tested by trained experimenters, have been placed upon record in the TRANSACTIONS of this Association (1911, pages 169 to 175) and elsewhere.[1] In these communications, dating from 1892 on, he has given due credit to the long-standing traditions of the profession and to the clinical workers who have before him and contemporaneously advocated plans of treatment somewhat similar, so far, at least, as the use of quinine compounds is concerned—and of whom Juergensen (1871), Schultz (1886), Aufrecht and Petzold (1902), Henry (1903), and Galbraith (1904), may again be named.

In the present research, clinician and laboratory worker have

* Through the courtesy of Prof. Allen J. Smith this work has been done in the Laboratory of Experimental Pathology of the University of Pennsylvania.

The full paper with additional tables and detailed descriptions will appear in the Journal of Infectious Diseases.

coöperated thoroughly and continuously. The problems had long ago been definitely formulated, as the result of observation at the bedside, and although considerable valuable work had, meanwhile, been done by others, as partially set forth in the appended bibliography,[2] it was thought best to work independently from the beginning along our own lines, even if previous observations should thereby be repeated. Comparison and confirmation of results is also worth while. Moreover, our research, as a whole, involves certain problems as yet not touched upon in reported experiments, and in order that conclusions may be dependable, consistent methods must be employed throughout. The actual technical work of experimentation has necessarily been done by the laboratory worker (J. A. K.), and he desires to acknowledge the assistance, in certain observations, of Dr. George D. Heist.

The present report is concerned with a single phase of the investigation, but involves a number of related problems: (1) Do quinine and its compounds and congeners possess any special germicidal power (bacteriotropism) over pneumococci, and if so, to what extent? (2) Granting this power, is there any, and if so how much, difference among the various basic cinchona derivatives and the various compounds of these bases? (3) Is there any difference in resistance to any or all of the drugs tested among the various serological types of pneumococci?

The problem of modification of the molecule, partially solved by Morgenroth in the production of optochin (ethylhydrocupreine), was not directly considered in this particular phase of the work, but is taken up elsewhere.*

Types I, II, and III of the pneumococcus were selected for study. Optochin (ethylhydrocupreine) and its hydrochloride, hydroquinine (methylhydrocupreine) and its hydrochloride, quinine, and its monobasic and dibasic salts with sulphuric, hydrochloric, and

* Cupreine is found in the Cuprea (*Remijia pedunculata*) bark and hydroquinine with quinine in the Cinchona bark. The chemical relationship of the cupreine group to the quinine group is indicated by the following formulas:

Cupreine	$C_{19}H_{20}N_2.OH.OH$
Quinine	$C_{19}H_{20}N_2.OH.OCH_3$
Hydrocupreine	$C_{19}H_{22}N_2.OH.OH$
Methylhydrocupreine (hydroquinine)	$C_{19}H_{22}N_2.OH.OCH_3$
Ethylhydrocupreine (optochin)	$C_{19}H_{22}N.OH.OC_2H_5$
Quinethylin (according to Grimaux and Arnaud)	$C_{19}H_{22}N_2.OH.OC_2H_5$

hydrobromic acids, its salicylate, arsenate, lactate, valerinate, and tannate, and the double hydrochloride of quinine and urea—the last named being that preferred by the clinician in his therapeutic work—were the drugs investigated.* This seemed to give a sufficiently wide range for the development of factors of modification. Some of the modifications observed, especially as regards quinine dihydrobromide and quinine arsenate, are suggestive in many directions.

Multitudinous observations were made, all conducted or personally confirmed by one of us (J. A. K.); but only a partial summary is here reported. After it had been determined that the three types of pneumococci gave approximately equivalent results, some experiments, to save time, were confined to a single type, since the point to be determined was independent of type. So, too, in certain observations only the most important compounds were used (or, in some instances, reported upon) since the individual differences were, for the particular purpose in view, relatively unimportant.

What has been chiefly in mind as regards comparison of agents has been (*a*) the differences between ethyl- and methyl-hydrocupreine, and between these and quinine, (*b*) the differences between quinine the alkaloid and its salts in general, (*c*) the differences between quinine and urea hydrochloride and other quinine compounds, (*d*) the relative influence of the acid radical in the sum total of influence of any compound, (*e*) the influence and relative importance of solubility. Concerning (*d*) and (*e*) further study is necessary.

The tests have been made according to the following methods:

I. Germicidal Tests. This implies *brief exposure* of *large numbers* of microörganisms to relatively *high concentrations* of the chemical tested.

(A) *Centrifuge Method.* The cultures being well established, were exposed for one hour at 37° C., to the action of varying dilutions of the agents tested; after removal of cocci and washing by centrifugalization, they were again cultured for forty-eight hours. Only

* We are indebted to the Powers, Weightman, Rosengarten Co. for the gift of the quinine compounds used in the study.

those compounds could be used which gave clear solutions in the concentrations employed. The results are set forth in Table I following:

TABLE I.—RESULTS OF BACTERICIDAL TESTS WITH THE CENTRIFUGE METHOD

Substance.	Dilution killing in one hour. Type I.	Type II.	Type III.
Ethylhydrocupreine hydrochloride	1:800	1:700	1:700
Quinine and urea hydrochloride	1:100	1:200	1:150
Hydroquinine hydrochloride	1:100	1:100	1: 80
Quinine bisulphate	1:100	1: 80	1: 80
Quinine dihydrochloride	1:100	1:120	1:100
Quinine hydrobromide	1:100	1:100	1:100

(B) *Combined in Vitro-vivo Method.* Large numbers of highly virulent pneumococci of type I were exposed to high concentrations of the drug to be tested, in a salt solution, for periods of five, fifteen, thirty, forty-five and sixty minutes respectively. At the end of each of these periods the effect of the bactericide was tested by intraperitoneal injection of small amounts of the drugged cultures into white mice. Fairly constant and decisive results were obtained and are summarized in Tables II (p. 378) and III (p. 379).

In these experiments concentrations greater than the maximum points of solubility of the particular salts under test were sometimes used, but the presence of undissolved particles did not appear to interfere with the regularity of the results. The animals were kept under observation for six days, but the tables show the results observed within forty-eight hours. After this, as shown by necropsy and bacteriological study, death sometimes occurred from drug poisoning rather than infection.

II. ANTISEPTIC TESTS. *Small numbers* of microörganisms are exposed to *weak dilutions* of the disinfectant over a *long period* of time. This form of test brought out clearly the efficacy and high degree of specificity of cinchona derivatives as pneumococcicides.

(A) *Tube Method.* The tests were conducted at 37° C., with varying solutions of the drug in broth, these solutions being inoculated with a fixed amount of virulent culture. The results shown in Table IV (p. 379) were noted after eight days; it having been found that in certain instances solutions remaining unclouded for twenty-four hours or longer subsequently appeared to permit

pneumococcal growth. No tabulation of the evident retarding effect is presented, but the general observation is placed on record.

TABLE II.—RESULTS OF THE COMBINED IN VITRO-VIVO METHOD (PNEUMOCOCCUS TYPE I, M. L. D. FOR MICE 0.0000001 C.C. OF TWENTY-FOUR-HOUR BROTH CULTURE) WITH CINCHONA DERIVATIVES

Substance.	Dilution.	Exposure in minutes.				
		5	15	30	45	60
Ethylhydrocupreine hydrochloride	1: 1000	–	–	–	–	–
	1: 2000	Died	–	–	–	–
	1: 10,000	Died	Died	Died	Died	Died
Quinine and urea hydrochloride	1: 100	–	–	–	–	–
	1: 500	Died	Died	–	–	–
	1: 1000	Died	Died	Died	Died	Died
Hydroquinine hydrochloride	1: 100	–	–	–	–	–
	1: 500	Died	Died	Died	–	–
	1: 1000	Died	Died	Died	Died	–
Quinine bisulphate	1: 200	Died	–	–	–	–
	1: 1000	Died	Died	Died	Died	Died
Quinine hydrochloride	1: 100	–	–	–	–	–
	1: 500	–	–	–	–	–
	1: 1000	Died	–	–	–	–
Quinine lactate	1: 200	–	–	–	–	–
	1: 500	Died	Died	–	–	–
	1: 1000	Died	Died	Died	Died	Died
Quinine salicylate	1: 100	–	–	–	–	–
	1: 500	Died	–	–	–	–
	1: 1000	Died	Died	Died	Died	–
Quinine arsenate	1: 200	–	–	–	–	–
	1: 500	Died	Died	–	–	–
	1: 1000	Died	Died	Died	Died	Died
Quinine (alkaloid)	1: 100	–	–	–	–	–
	1: 200	–	–	–	–	–
	1: 500	Died	Died	–	–	–
	1: 1000	Died	Died	Died	Died	Died
Controls	.....	Died	Died	Died	Died	Died

(B) *Plating Method.* The bactericide in varying dilutions was allowed to remain in contact with the cocci for a period of twenty-four hours at 37° C., when subcultures were made in 10 c.c. of blood agar. The particular advantage of this method lies in its

power to show, under identical conditions, both the inhibiting (or *antiseptic*) and the killing (or *germicidal*) doses of the chemical studied. The results are shown in Table V (below).

TABLE III.—RESULTS OF THE COMBINED IN VITRO-VIVO METHOD (PNEUMOCOCCUS TYPE I) WITH OTHER THAN CINCHONA COMPOUNDS

Substance.	Dilution.	Exposure in minutes.				
		5	15	30	45	60
Phenol	1:100	—	—	—	—	—
	1:200	Died	Died	Died	—	—
	1:500	Died	Died	Died	Died	Died
Mercuric chloride	1:100	—	—	—	—	—
	1:200	Died	Died	—	—	—
	1:500	Died	Died	Died	Died	—
Controls	.....	Died	Died	Died	Died	Died

TABLE IV.—SUMMARY OF RESULTS WITH THE ANTISEPTIC (TUBE) METHOD AND DIFFERENT TYPES OF PNEUMOCOCCI, SHOWING THE DILUTIONS WHICH INHIBITED GROWTH FOR EIGHT DAYS

Substance.	Pneumococci. Type I. 1:	Type II. 1:	Type III. 1:
Ethylhydrocupreine hydrochloride	1,000,000	2,000,000	1,500,000
Hydroquinine hydrochloride	80,000	50,000	20,000
Quinine and urea hydrochloride	10,000	20,000	16,000
Quinine (alkaloid)	20,000	50,000	20,000
Quinine bisulphate	80,000	80,000	100,000
Quinine tannate	20,000	20,000	5,000
Quinine dihydrobromide	100,000	100,000	20,000
Quinine arsenate	100,000	200,000	100,000
Quinine salicylate	50,000	100,000	100,000
Quinine dihydrochloride	50,000	20,000	20,000
Quinine valerianate	50,000	80,000	16,000
Quinine sulphate	200,000	100,000	20,000
Quinine hydrobromide	200,000	100,000	20,000
Quinine phosphate	100,000	80,000	20,000
Quinine lactate	100,000	100,000	20,000

TABLE V.—SUMMARY OF THE RESULTS OF THE PLATING METHOD SHOWING THE BACTERICIDAL ACTION OF CINCHONA DERIVATIVES (AND OF UREA HYDROCHLORIDE) UPON PNEUMOCOCCUS TYPE I

	Highest dilution causing. Inhibition 1:	Sterility 1:
Ethylhydrocupreine hydrochloride	1,000,000	40,000
Hydroquinine hydrochloride	60,000	7,000
Quinine and urea hydrochloride	60,000	6,000
Quinine bisulphate	40,000	5,000
Quinine hydrochloride	40,000	4,000
Urea hydrochloride	not in 100	not in 100

III. Serum and Salt Comparison. This was carried out by the *pipet* method of Wright. Varying dilutions of the drug were prepared in sterile normal (human or horse) serum in amounts of 1 c.c. in a series of small sterile tubules held in a slanting position in plasticine and inoculated with 0.2 c.c. of a twenty-four-hour broth culture of pneumococcus. At intervals of five, ten, fifteen, twenty, and thirty minutes each dilution was subcultured by drawing a small quantity, averaging about 5 cm., into the pipet, the bulb of which had been filled, just before, with a special pneumococcus blood-dextrose broth. The pipet was immediately sealed in a flame and incubated for forty-eight hours. The results are shown in Table VI following:

Table VI.—Results of Comparative Bactericidal Tests in Serum and Salt Solution with the Pipet Method (showing also Comparison of Cinchonics with other Chemicals)

Substance.	Dilution killing in thirty minutes. In serum.	In salt solution.
Ethylhydrocupreine hydrochloride	1: 20,000	1: 100,000
Quinine and urea hydrochloride	1: 200	1: 250
Hydroquinine hydrochloride	1: 500	1: 750
Quinine bisulphate	1: 300	1: 500
Quinine hydrochloride	1: 100	1: 500
Quinine tannate	1: 30	1: 50
Quinine dihydrobromide	**1: 1000**	**1: 500**
Quinine salicylate	1: 300	1: 500
Phenol	1: 150	1: 300
Mercuric chloride	1: 1000	1: 10,000

Horse serum and human serum were shown by control tests to be without appreciable bactericidal influence.

IV. Cross-tests. The specificity of the bactericidal action of cinchona derivatives on pneumococcus was studied (*a*) by cross-testing their efficacy against Bacillus typhosus and Staphylococcus aureus; (*b*) by testing the bactericidal activity of mercuric chloride, arsenobenzol, and other chemicals upon pneumococci. In what we have termed the germicidal tests (large numbers of organisms, strong solution, brief exposure), phenol and mercuric chloride compare favorably with the ordinary run of quinine compounds, though far inferior to the hydrocupreine compounds. By the antiseptic method (small numbers of organisms, weak solutions, long exposures), not only are quinine and optochin shown to possess a

much higher degree of bactericidal activity over the pneumococcus than over other organisms, but also the other chemicals are shown to be far inferior to quinine and optochin in power over the pneumococcus.

The *germicidal* results are shown in Tables II and III (pages 379 and 380) and Table VI (page 381). The results of the *antiseptic* method are shown in Table VII following:

TABLE VII.—SUMMARY OF RESULTS WITH THE ANTISEPTIC (TUBE) METHOD WITH CINCHONICS AND OTHER DISINFECTANTS UPON VARIOUS MICROÖRGANISMS

Substance.	Dilutions and organisms. Pneumococcus. Type I.	Bacillus typhosus.	Staphylococcus. aureus.
Ethylhydrocupreine hydrochloride	1: 1,000,000	1: 2500	1: 5000
Quinine and urea hydrochloride	1: 10,000	1: 2000	1: 2000
Hydroquinine hydrochloride	1: 50,000	1: 2000	1: 2000
Quinine bisulphate	1: 80,000	1: 1000	1: 2000
Quinine dihydrobromide	1: 100,000	1: 2000	1: 1000
Quinine salicylate	1: 50,000	1: 1000	1: 1000
Quinine tannate	1: 20,000	1: 1000	1: 1000
Quinine (alkaloid)	1: 20,000	1: 2000	1: 1000
Arsenobenzol	1: 2,500	1: 2000	1: 1000
Phenol	1: 1,000	1: 125	1: 80
Mercuric chloride	1: 5,000	1: 20,000	1: 20,000
Urea hydrochloride	Not in 1: 100	Not in 1: 100	Not in 1: 100
Salicylic acid	1: 1,000	Not tested	Not tested.
Sodium salicylate	1: 300	Not tested	Not tested.
Hydrochloric acid	1: 100	Not tested	Not tested.

Results as to Types of Pneumococci. Variations in resistance to bactericidal agents among cultures of the same serological type of pneumococcus are in some instances marked. This is illustrated in the summary (Table VIII, p. 383) of some selected results with types I and II. (In our general summaries we have always taken the lowest figures obtained.)

Apart from this, the various tables show, as has been found by other observers, that the activity of any given cinchona derivative against serological types I and II is approximately the same, while type III seems to show in many instances a distinctly, if but slightly, greater resistance.

Results as to the Acid Radical. A certain number of tests were made to determine the influence of the acid radical in quinine compounds. Urea hydrochloride was shown to be inactive in concen-

tration, so great as 1 to 100. Hydrochloric acid was inactive in less concentration than 1 to 100; sodium salicylate in less than 1 to 300, and salicylic acid in less than 1 to 1000. So far as these agents are concerned, therefore, almost the total germicidal activity over the pneumococcus of their compounds with quinine belongs to ths cinchona constituent only. Other observations along these lines are in progress, but we are not yet ready to report. The differences in power in special instances among the different salts, the lack of uniformity in different experiments and in tests by different methods, all need further study. It seems clear, however, that apart from any question of solubility, the powers of the various quinine compounds *do not*, as might have been presumed, vary according to the percentage of alkaloid present.

Other explanations are to be sought.

TABLE VIII.—VARIATION IN RESISTANCE TO BACTERICIDAL AGENTS AMONG CULTURES OF THE SAME TYPE OF PNEUMOCOCCUS

Substance.	Method.	Highest killing dilution.			
		Type I.		Type II.	
		A. 1:	B. 1:	A. 1:	B. 1:
Ethylhydrocupreine hydrochloride . . .	Antiseptic	1,000,000	1,500,000	2,000,000	3,200,000
	Plating	40,000	20,000	80,000	120,000
	Pipet*	100,000	200,000	150,000	120,000
Hydroquinine hydrochloride . . .	Antiseptic	80,000	60,000	50,000	100,000
	Plating	6,000	14,000	8,000	10,000
	Pipet	500	400	600	1,000
Quinine and urea hydrochloride . . .	Antiseptic	10,000	40,000	20,000	30,000
	Plating	6,000	8,000	8,000	8,000
	Pipet	200	200	250	400

It is to be borne in mind, also, that we are dealing here purely with the inhibiting and killing effects upon pneumococci, and not with any of the other factors concerned in the clinical results of the use of quinine or of optochin in pneumonia. Some of these latter have been, and others will be, made the subject of special studies, which are to be reported in other communications.

Our general conclusions from this phase of our research may thus be summarized:

* In serum in all tests.

CONCLUSIONS. 1. Certain cinchonics [*i. e.*, quinine, hydroquinine (methylhydrocupreine) and optochin (ethylhydrocupreine) and their salts] exert a very high bactericidal power upon pneumococci *in vitro*, ethylhydrocupreine being enormously the most active (*e. g.*, by the antiseptic method, optochin is effective in dilutions averaging 1 : 1,500,000, as compared with an average of about 1 : 80,000, of the various quinine compounds). Similar studies of other cinchona alkaloids with their compounds and derivatives are to be desired.

2. The results of bactericidal tests, numerically expressed, vary greatly according to the technic employed and according to such factors as the temperature, duration of exposure, and vigor and virulence of the test microörganism. It is important, therefore, to compare only results obtained with identical technic and under stated and standard conditions.

3. While the relative bactericidal values of the various cinchona derivatives exhibit considerable differences among the agents, it is probable that the power of any one agent is about the same for all types of pneumococci, although type III (Pneumococcus mucosus) was found somewhat more resistant in certain instances, than the other two types studied. The fact that the different quinine compounds *do not*, as might have been presumed, appear to vary in bactericidal activity according to their alkaloidal content, makes needful a further investigation of the relative influence of acidic and basic radicals and of the molecule as a whole.

4. Different cultures of pneumococci belonging to the same serological type exhibit varying degrees of resistance to bactericidal agents. It is probable that this variation bears a relation to virulence, and more particularly as to whether the strain has been freshly isolated from human or experimental lesions or has been cultivated for a prolonged period on artificial media.

5. The cinchonics studied act slowly upon pneumococci, and the best bactericidal and inhibiting values (*i. e.*, the most marked activity of *high dilutions—circa* 1 : 10,000 to 1 : 2,000,000) are found when the number of microörganisms is small, and the exposure relatively prolonged. Nevertheless, even with brief exposures (5 to 60 minutes) and large numbers of virulent microörganisms,

moderately high concentrations (*Circa* 1 : 100 to 1 : 2000) were germicidal.

6. Cross-bactericidal tests—using, on the one hand, quinine and optochin compounds, with cultures of Bacillus typhosus and of a staphylococcus; and, on the other hand, arsenobenzol, phenol, mercuric chloride, sodium salicylate, and other substances with cultures of pneumococci—show that the cinchona derivatives possess a high degree of specific pneumococcicidal activity.

7. The pneumococcicidal activity of optochin (ethylhydrocupreine) hydrochloride was reduced to one-fifth part in a menstruum of serum as compared with normal salt solution. The activity of the majority of the quinine salts tested was relatively but slightly reduced in serum, so that the apparent superiority of optochin was to a certain extent overcome. Exceptionally, quinine dihydrobromide showed an increased power in serum (100 per cent.). The suggestion thus given is obvious and deserves further inquiry. The activity of phenol in serum was reduced to one-half, and that of mercuric chloride to one-tenth, of their respective values in salt solution. For bactericidal chemotherapy it is desirable that agents to be used clinically maintain a high degree of germicidal power in serum in tests *in vitro*.

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DISCUSSION

Dr. F. G. Novy, Ann Arbor, asked Dr. Kolmer how he knows that the organisms tested were killed? Does he only know that they were not growing? In work of this kind it is necessary to determine whether a given substance is actually germicidal or merely inhibitory. Extraordinarily small amounts of certain substances will inhibit the growth of enfeebled organisms.

Dr. John A. Kolmer, Philadelphia, said that the actual death of the organisms was determined by subculturing and by peritoneal injections.

Dr. S. Solis Cohen, Philadelphia, said that this report is only a preliminary one, on a single phase of the problem, but the point so ably made by Dr. Novy had been kept in mind and necessary checks were kept throughout the work. He expressed the hope that Dr. Novy or others would take up the matter, not only to confirm or correct the results reported, but also to advance the work. So far as ethylhydrocupreine is concerned, this work, in the main, only confirms previous observers; but Dr. Cohen did not believe that results to date indicated any such clinical superiority over quinine, as the germicidal showing might indicate. In other words, bactericide is only a small portion of the chemotherapeutic or serotherapeutic problem in pneumonia. Toxic and antitoxic, phagocytic and cytolytic and still other processes, both defensive and offensive, are to be considered, together with their modifications by indirect as well as direct drug actions.

This study was undertaken, because of the results obtained clinically, and especially during the past twelve years, by the systematic use of quinine in pneumonia; results comparable with the best obtained by any other method. On clinical grounds, purely, the speaker had put forth the view that this was owing to an antitoxic, rather than a germicidal, effect of the drug. To prove or disprove this, or to find a basis for its amplification or correction in any of the many ways that might be suggested, is the most difficult part of the investigation, and he had frequently and publicly requested competent observers to look into the matter—a request now repeated.

SYPHILIS OF THE PANCREAS, WITH REFERENCE TO THE COINCIDENCE OF SYPHILITIC PANCREATITIS AND DIABETES

By ALDRED SCOTT WARTHIN, Ph.D., M.D.
ANN ARBOR, MICHIGAN

(Preliminary Report)

Syphilis of the pancreas is regarded as a very rare affection by practically all recent writers of text-books on pathology and internal medicine. In the very latest American text-book of pathology, MacCallum states that the pancreas is rarely involved in acquired syphilis; and in the Osler-McCrae *Modern Medicine* Opie, in his paragraph on "Syphilis of the Pancreas," says that the pancreas is rarely the seat of gummata as the result of acquired syphilis and that there are no data with reference to the symptoms or diagnosis of syphilis of the pancreas. He does not even suggest the possibility that syphilis may be an etiological factor in the production of chronic interstitial pancreatitis—and hence possibly concerned in the causation of diabetes. All recent text-books and articles on syphilis make the same statements as to the extreme rarity of syphilitic disease of this organ.

These statements as to the rarity of syphilis of the pancreas are all based upon the old pathological criterion of syphilitic disease—*the gumma*. This is the pathology of forty years ago, and should be abandoned today when modern spirochete studies have shown that the *common pathology of syphilis is not the gumma but is a mild chronic interstitial inflammation leading to parenchymatous atrophy, degeneration and fibrosis*. It is the gumma that is rare; syphilitic inflammation and fibrosis are extremely common lesions, not only in the heart, aorta, and testes, but also in the pancreas. It will prob-

ably also be shown that such syphilitic inflammations are not uncommon in the stomach and other organs in which syphilis is now supposed to be of rare occurrence because gumma of these organs is rare. Likewise, in the nervous system the occurrence of gumma is relatively very rare compared to the destruction of nerve cells, proliferations of neuroglia, perivascular infiltrations, and sclerosis of vessels, due to the localization of Spirochæta pallida. My attention was first drawn to the occurrence of syphilitic inflammation of the pancreas by the fact that in 41 cases of latent syphilis studied by me there were 2 cases of diabetes in which the pancreas showed marked interstitial pancreatitis, both inter- and intralobular, with hyaline fibrosis of the islands of Langerhans. Spirochetes were demonstrated in the myocardium of both of these cases, and in 1 they were also found in the pancreas. Active syphilitic lesions were found in the myocardium, aorta, adrenals, and testes of these 2 cases.

Because of this coincidence of pancreatic syphilitic lesions and diabetes 4 other autopsy cases of diabetes occurring in our service since 1907 were studied and were found to show the same concurrence of syphilis. In 2 of these cases spirochetes were also found in active areas in the myocardium; the material from the remaining 2 cases was not examined by the Levaditi method, but active syphilitic inflammations were present in myocardium, aorta, and pancreas (and testes in 1 of these cases, the other being a female).

The diagnosis of syphilis in the 6 cases of diabetes was made upon histological changes alone in 2 cases; and in the other 4 cases upon the presence of precisely similar histological lesions in the heart containing the Spirochæta pallida, as shown by Levaditi's method. In 1 case similar histological lesions in the pancreas showed the presence of spirochetes. These same lesions were found in the pancreas in all 5 remaining cases; but no examination for spirochetes has as yet been carried out. Because of the pancreatic lesions found in these 6 cases of coincident syphilis and diabetes, the pancreas in each of the remaining 39 cases of latent syphilis was then more thoroughly studied, and it was found that this organ was not normal in any one of the old cases of syphilis, but that it presented a more or less severe pancreatitis. The study of the pancreas in latent syphilis,

as well as in active clinical cases, has been carried back in our autopsy material to embrace 150 cases of syphilis; and the same result has been obtained—not a single autopsy case of syphilis has shown a normal pancreas. The lesions vary greatly in extent and degree, but are essentially the same. They may be described as follows:

Pancreatic Changes in Latent and Active Syphilis. When the pancreas of each of the 6 cases was given a more detailed study than that made for the autopsy report, it was found that the pathological changes were essentially the same in all, but varying in degree. Briefly, these changes may be classified as follows:

1. Atrophy with fatty infiltration (fatty atrophy), involving particularly the tail and body of the organ.

2. Increase of stroma, both inter- and intralobular, particularly marked about the ducts, and extending along the intralobular ducts between the acini and presenting the picture of a chronic interstitial inflammation, is shown in all 6 cases. This is also most marked in the splenic end and body of the organ. The increase of stroma is not uniform but patchy. Normal lobules are side by side with lobules showing a marked fibrosis; and many sections from different blocks may show no increase of stroma at all. Large areas, particularly in the head, appear normal. The lobules showing the increase of stroma are smaller than normal, and contain adipose tissue cells. Occasionally completely fibroid areas are found in the more severe cases.

3. Inflammatory infiltrations, usually small in size, were found in every case, both in the interlobular connective tissue and within the lobules. The cells are almost wholly mononuclears, small and large lymphocytes, and plasma cells. Polynuclears and eosinophiles are rare. The seat of the infiltration is always in a loose, semifluid, proliferating connective tissue, resembling edematous connective tissue, and containing epithelioid fibroblastic cells. These areas are precisely like those in the myocardium containing colonies of spirochetes. In such active inflammatory areas were the spirochetes found in Case III.

4. Changes in the islands of Langerhans were present in all 6 cases. In all, the islands are undoubtedly greatly diminished in

number; in 2 cases only a few islands remained. Particularly in the tail of the organ is the total or nearly total disappearance of the islands notable. In 2 cases the remaining islands showed a marked hyaline fibrosis. Opie's hyaline degeneration of the cells of the islands was not seen in any case. The islands are destroyed by a connective-tissue proliferation which soon becomes fibroid and hyaline. A number of hypertrophic islands were seen in 1 case. No inflammatory infiltrations were found about the islands. It is clear that the destroyed islands are replaced by irregular masses of fibrous tissue showing no remains of the island structure.

5. The acini in all 6 cases also showed marked changes. In many lobules atrophic acini are present, particularly in those showing marked fibrosis. The majority, however, are larger than normal, this increase in size being very marked in many lobules. The nuclei are larger and the protoplasm shows a marked increase of zymogen granules. Occasionally acini with hyaline protoplasm staining deep red with eosin are found.

6. Numerous structures looking like newly formed islands are found in the areas showing most marked fibrosis and inflammation. At first glance they were interpreted as such. Minute study showed them to be new-formed lobules of acini arising from the ducts. Their origin from the epithelium of the latter can be easily demonstrated. In some cases they have been seen developing inside large dilated ducts. In their earlier stages they very much resemble the islands of Langerhans, because of the small size of their cells, collapsed lumina, and deeply staining nuclei; but centro-acinar cells are found within the undeveloped lumen of the acinus, and they have not the vascular arrangement of the islands. All stages can be traced between these newly formed lobules and large adenoma-like structures with dilated lumina containing centro-acinar cells. They undoubtedly represent regenerative attempts, a new formation of acini from the duct epithelium. In these 6 cases I have found no positive evidence of any new formation of islands. In 1 case (Case VI) very large islands were found and were interpreted as hypertrophic.

7. The bloodvessels show in all cases varying degrees of sclerosis.

8. The ducts are often dilated and show thickened walls. Cystic

ducts are present in every case, and are probably retention cysts of intralobular ducts due to the fibrosis. In one of these papilliferous growths were seen.

The essential pancreatic pathology is the same in all of the 150 cases of latent syphilis, congenital or acquired. There is in all a more or less diffuse or patchy pancreatitis and fibrosis, both interlobular and interacinar. There is a more or less marked atrophy of the organ, usually associated with fatty infiltration of the stroma. With these changes there is marked disappearance of the islands of Langerhans with hyaline fibrosis of the islands. Opie's hyaline degeneration of the islands was not seen in any case. The hyalin of the islands is connective-tissue hyalin—a fibrosis with hyaline change in the connective tissue. Localized lymphocyte and plasma-cell infiltrations occur in all, from very slight collections up to large areas. Fibroblastic proliferation of the stroma occurs within and between the lobules. The rudimentary lymphoid nodes are hyperplastic. Compensatory hypertrophy and regenerative new-formation of acini from the ducts is found in practically all cases. No new-formation of islands was observed, although apparently hypertrophic islands occur in many cases. The newly formed acini in certain stages very closely resemble islands, and such new-formations have no doubt been frequently interpreted as new islands. This is probably true of the illustration shown in Opie's article in *Modern Medicine*. The structures shown there as new-formed islands, are, I feel sure, only newly formed acini. Close study will show the presence of intra-acinar cells and the absence of the vascular relations of the island.

The degree of extent and severity of these changes varies in all cases. In the most severe cases there may be a most marked fibrosis of the gland with but little normal pancreatic tissue remaining. In the majority of cases the process is essentially patchy and scattered. Normal lobules are found side by side with those showing very marked interstitial fibrosis and atrophy. Many sections from different portions of the gland may have to be examined before areas of pancreatitis are found. Such areas are always more numerous in the tail and body of the organ than in the head.

Two important questions at once arise: Are these changes char-

acteristic of syphilis; and what is their relation to diabetes. It is certainly interesting and suggestive, to say the least, that in 150 cases of old latent syphilis there should be 6 cases of diabetes in which the pancreas showed precisely the same pathological changes as are found in this organ in the other cases of syphilis. Is this coincidence purely one of chance?

As to the specificity of the histological changes, I believe that the active areas of lymphocyte and plasma-cell infiltration, with slight fibroblastic proliferations frequently myxomatous in type, with vascular proliferations and obliterations, are in themselves sufficiently characteristic to warrant a diagnosis of latent syphilis from the histological picture above. I know of no other etiological factor for these histological changes. They occur in the bodies of all syphilitics. I have never found them in any other form of infection or intoxication. They are precisely similar to the changes found in the meninges, myocardium, aorta, adrenals, testes, intestinal wall, mesentery, etc., in which spirochetes have been repeatedly demonstrated; and in 1 case we have found spirochetes in these pancreatic lesions. The ultimate fibrosis may be the same as that resulting from arteriosclerosis, due to lead-poisoning, age, etc., but the active areas are, to my knowledge, characteristic of spirochete localization and action. In a number of cases of advanced arteriosclerosis, in which no active lesions of syphilis could be found anywhere in the body after ordinarily careful routine examinations, interstitial fibrosis and sclerosis of the pancreas were also present. It is impossible to say in the absence of active areas that these changes were not of syphilitic origin. The question of the existence of a non-syphilitic arteriosclerotic fibrosis of the pancreas must, therefore, still be an open one.

This fact remains: The pancreas in all cases of latent syphilis is affected in the same way that all other organs and tissues are involved in the general infection. Latent syphilis is a general process; its lesions occur in all organs, more marked in certain organs as the heart wall, aorta, pancreas and testis, in all cases; while in individual cases certain organs (brain, cord, etc.,) are more severely involved. But the heart, aorta, pancreas, adrenals and testes of the paretic and tabetic always show syphilitic lesions and spirochete

localizations. Nothing is of greater importance for the clinician to recognize at the present time than the fact that *old syphilis means generalized infection;* and that pathological lesions occur in all organs. *But these lesions are not gummas; they are slight, mild, very chronic interstitial inflammations with corresponding atrophy and parenchymatous degenerations.*

I believe that syphilis is the most common cause of *chronic interstitial pancreatitis,* and that such pancreatic lesions will be found in the pancreas of all cases of old latent syphilis. Only one other pathologist seems to have recognzied this; C. Steinberg (*Aschoff's Pathologische Anatomie,* Band ii) says that syphilis leads frequently to interstitial inflammation and induration of the pancreas. As to the etiological relationship of syphilitic pancreatitis to diabetes mellitus, the problem must still be considered unsettled. Apparently just as marked interacinar pancreatitis and fibrosis, with hyaline changes and disappearance of the islands, occurs in *non-diabetic* syphilitics as in the diabetics. It is, of course, very difficult to estimate comparatively the degree of change in a given pancreas by the examination even of a large number of sections made from different portions of the organ. Complete serial section-studies of the pancreas from diabetic and non-diabetic syphilitic cases might reveal that in the former the degree of change is greater than in the latter. Or perhaps, after all, the pancreatic changes in themselves are not the only factor responsible for the development of the diabetic complex, and that possibly associated changes in liver, adrenals, hypophysis, etc., may be necessary to produce the diabetic phenomena.

In conclusion, the pancreas always shows lesions in old latent syphilis, acquired or congenital. Syphilis is the most common cause of the interstitial interlobular and interacinar pancreatitis with fibrosis and disappearance of the islands of Langerhans so frequently associated with diabetes that some writers have regarded it as part of the essential pathology of this affection. The exact relationship of this pancreatic pathology to diabetes is, however, still an unsettled problem.

COAGULATION TIME IN LOBAR PNEUMONIA, WITH STATISTICS AND AN EXPERIMENTAL STUDY OF ITS CAUSES

By J. M. ANDERS, M.D.

AND

GEORGE H. MEEKER, Ph.D., Sc.D.

(By Invitation)

The etiological factors concerned in coagulation of the blood are still imperfectly understood.[1] It is common knowledge that the time necessary for coagulation to occur is variable, and depends upon many conditions. That bacteria and their toxins play a role in the coagulation process is undoubted, but their significance is not definitely known. Nevertheless, the subject of the relation of infection to coagulation has been discussed by not a few modern writers, and on the whole the weight of authority is in favor of the view that infectious diseases retard coagulation.

The coagulative process is known to be a complex one, involving in its first stage the action of thrombokinase upon prothrombin in the presence of soluble calcium salts producing thrombin. The blood plasma also contains a protein known as fibrinogen, which is acted upon by the thrombin when blood is shed, forming fibrin. It has been definitely shown that the plasma within the bloodvessels differs from the serum resulting from coagulation in that it contains fibrinogen, unlike the latter.

[1] With thrombosis and agglutination—processes which are more or less closely allied to coagulation—the present discussion is not directly concerned. A comprehensive discussion on the subject of "Prothrombin and Antithrombin Factors in the Coagulation of Blood" has been thoroughly investigated and reported on by Minot, Denny and Davis, Archives of Internal Medicine, January, 1916, p. 101.

In pneumonia it has long been currently stated, although denied by some recent writers, that the coagulative period is shortened, due to the richness and density of the fibrin network. The fibrin factors of the blood are greatly increased in this disease, "the proportion rising from 4 to 10 parts per thousand."

When normal blood coagulates, "about 0.1 to 0.4 per cent. of its weight separates as fibrin" (Krehl).[1] In certain diseases, especially those accompanied by inflammatory exudates (*e. g.*, lobar pneumonia, pleurisy) a marked pathological increase up to 1 per cent. or over may be found. In certain infections, notably typhoid fever, no increase is observed, although intravascular clotting is more common in this disease than in lobar pneumonia if we except the large so-called marantic thrombi found in the great vessels after death.

That the quantity of the fibrin factors has nothing to do with either extra- or intravascular clotting is further shown by the fact that they are present in normal amount in hemophilia (Litten, Sahli).

The coagulation time is found to be shortened after hemorrhage (severe pulmonary hemorrhage, hematuria), in carcinoma of the uterus, in abortion, after transfusion, in endocarditis, in dementia precox and after the administration of gelatin.

A considerable number of tests to determine the coagulation period of the blood, most of them accurate enough for ordinary purposes, have been advanced. The method employed by us is known as Bogg's test. In taking specimens of blood from healthy persons and also from subjects ill of pneumonia, the finger tips and ear lobes, mainly the former, were used. The parts were thoroughly cleansed with water, followed by alcohol and then allowed to dry and the puncture made deep enough to cause a free flow of blood.

Lee and White[2] have pursued the method of withdrawing 1 c.c. of blood from an arm vein, using a small all-glass syringe (for example, Burroughs and Wellcome, 20 m.), preferably with a platinum needle, this syringe having first been sterilized and rinsed out with normal salt solution. This method "obviates the contact of blood

[1] Clinical Pathology, 1907, p. 169.
[2] Amer. Jour. of the Med. Sc., April, 1913.

with tissue juice," which contains thrombokinase. Our observations were made daily in order to obtain an accurate average coagulation time, and it was feared that an unwarranted degree of discomfort would be caused by venipuncture at intervals of twenty-four hours in patients suffering from lobar pneumonia.

We have endeavored to throw a sidelight on the question of the duration of the coagulation time in lobar pneumonia, and in order to accomplish this object an examination of both pneumonic and normal bloods was made; the same method having been employed in both cases.

TABLE 1

Case No.	Age.	Sex.	Average coagulation time.		Average leukocyte count, before crisis.	Termination.	Remarks.
			Before crisis.	After crisis.			
1. M. P.	19	M.	3.55	..	21,200	Death	Developed pneumothorax.
2. F. T.	41	M.	6.25	5.50	17,100	Death	Crisis on 9th day; empyema on 13th; operation; pneumococcic and streptococcic infection of pleura.
3. M. D.	53	F.	4.40	4.45	19,400	Recovery	
4. J. H.	47	F.	4.00	..	24,600	Death	
5. J. G.	32	M.	3.00	2.30	15,500	Recovery	Ether pneumonia followed enucleation of eye.
6. M. R.	14	F.	2.40	2.40	26,000	Recovery	
7. M. R.	32	F.	3.05	4.05	18,000	Recovery	Marked dry pleurisy; delirious for day or two after crisis.
8. R. C.	23	F.	2.30	..	22,200	Death	Pneumonia beginning during labor; no crisis.
9. W. P.	18	M.	3.0	3.20	16,000	Recovery	
10. S. P.	23	F.	3.35	4.50	20,800	Recovery	Pregnant about $7\frac{1}{2}$ mos.
11. J. D.	55	M.	2.25	..	12,400	Death	Complicating delirium tremens; coagulation on day of death.
12. E. G.	21	F.	3.45	..	7,800	Recovery	Aortic regurgitation and serofibrinous pleurisy; no complications.
13. H. D.	67	M.	3.45	3.30	18,000	Recovery	
14. G. B.	35	F.	1.0	3.05	15,400	Recovery	
15. T. H.	17	M.	1.40	4.20	18,900	Recovery	Healed tuberculous bone lesion.
16. L. R.	19	M.	2.50	4.55	17,800	Recovery	Crisis delayed to 18th day, by migration to opposite side.
Average	32	..	3.15	4.0	18,200		

The accompanying table (No. 1) sets forth the age, sex, average coagulation time before and after the crisis, average leukocyte count, remarks, etc., of 16 cases of pneumonia treated during the past winter in the Medico-Chirurgical Hospital. The coagulation time was noted daily both before and after the crisis, and then the average duration carefully estimated.

The total number of observations was 138, and the coagulation time ranged from one minute to six minutes and forty-five seconds. A comparison of the figures with those of Table No. 2 will show that the coagulation time is distinctly shorter, as a rule in pneumonia, than in healthy individuals, *i. e.*, a mean difference of one minute and fifty-five seconds.

Rudolph and Cole[1] made 47 observations upon 17 cases of lobar pneumonia and found the average clotting time to be 8.1 minutes, but ranged from 5.5 to 12.75 minutes.

A comparison of the findings tabulated in Table No. 2 with those of Table No. 3 is of some interest as showing the effect of mealtime (mixed diet) upon the coagulative process.

It will be observed that the coagulation time is, on the whole, but slightly influenced by the ingestion of a meal. Thus in two series of 100 cases each the average duration of this period was only 12 seconds longer in the group in which the tests were made two or more hours after food.

It was found that the tests made within two hours after food ranged from 3 minutes and 55 seconds to 7 minutes and 10 seconds, while the estimated average for the entire series (100 cases) was 4 minutes and 58 seconds. The tests made after two hours following a meal showed a range from 4 minutes and 25 seconds to 6 minutes and 20 seconds, averaging 5 minutes and 10 seconds.

To account for the abbreviated coagulation time in pneumonia, as shown by the above statistical results, the question naturally arises, Does the action of the pneumotoxins circulating in the blood transform prothrombogen (normally found in the walls of the bloodvessels and in the lymph nodes) into thrombin, or in some manner other than this, modify the factors which govern

[1] Amer. Jour. Med. Sc., April, 1913, p. 481.

coagulation? So far as concerns the laboratory evidence, this query, however, can be answered in the negative.

TABLE 2.—COAGULATION TIME WITHIN TWO HOURS AFTER MEALTIME

Observ. No.	Date.	Coagulation time.	Observation No.	Date.	Coagulation time.
1	Feb. 2, 1916	5 min. 20 sec.	51	Feb. 26, 1916	4 min. 55 sec.
2	Feb. 2, 1916	4 " 45 "	52	Feb. 26, 1916	5 " 40 "
3	Feb. 2, 1916	5 " 40 "	53	Feb. 27, 1916	5 " 00 "
4	Feb. 2, 1916	4 " 20 "	54	Feb. 28, 1916	4 " 30 "
5	Feb. 3, 1916	5 " 00 "	55	Feb. 28, 1916	4 " 50 "
6	Feb. 3, 1916	4 " 40 "	56	Feb. 28, 1916	6 " 05 "
7	Feb. 5, 1916	7 " 10 "	57	Feb. 28, 1916	4 " 10 "
8	Feb. 5, 1916	5 " 50 "	58	Feb. 28, 1916	4 " 45 "
9	Feb. 5, 1916	4 " 30 "	59	Feb. 28, 1916	5 " 30 "
10	Feb. 5, 1916	5 " 20 "	60	Feb. 28, 1916	4 " 40 "
11	Feb. 7, 1916	4 " 00 "	61	Feb. 29, 1916	5 " 00 "
12	Feb. 7, 1916	6 " 10 "	62	Feb. 29, 1916	5 " 40 "
13	Feb. 7, 1916	5 " 30 "	63	Feb. 29, 1916	6 " 00 "
14	Feb. 7, 1916	5 " 00 "	64	Mar. 1, 1916	4 " 55 "
15	Feb. 7, 1916	5 " 20 "	65	Mar. 1, 1916	5 " 20 "
16	Feb. 7, 1916	4 " 30 "	66	Mar. 1, 1916	5 " 05 "
17	Feb. 9, 1916	6 " 10 "	67	Mar. 1, 1916	4 " 30 "
18	Feb. 9, 1916	5 " 20 "	68	Mar. 1, 1916	4 " 25 "
19	Feb. 9, 1916	4 " 40 "	69	Mar. 1, 1916	5 " 50 "
20	Feb. 9, 1916	4 " 55 "	70	Mar. 1, 1916	4 " 10 "
21	Feb. 9, 1916	4 " 30 "	71	Mar. 2, 1916	5 " 30 "
22	Feb. 10, 1916	5 " 50 "	72	Mar. 2, 1916	4 " 50 "
23	Feb. 10, 1916	4 " 10 "	73	Mar. 2, 1916	4 " 10 "
24	Feb. 11, 1916	5 " 45 "	74	Mar. 2, 1916	4 " 35 "
25	Feb. 12, 1916	6 " 20 "	75	Mar. 2, 1916	5 " 00 "
26	Feb. 12, 1916	5 " 00 "	76	Mar. 4, 1916	4 " 30 "
27	Feb. 12, 1916	5 " 30 "	77	Mar. 4, 1916	4 " 55 "
28	Feb. 12, 1916	4 " 55 "	78	Mar. 5, 1916	5 " 50 "
29	Feb. 12, 1916	4 " 00 "	79	Mar. 6, 1916	6 " 15 "
30	Feb. 15, 1916	4 " 55 "	80	Mar. 6, 1916	5 " 20 "
31	Feb. 15, 1916	5 " 15 "	81	Mar. 6, 1916	4 " 10 "
32	Feb. 17, 1916	6 " 10 "	82	Mar. 6, 1916	4 " 55 "
33	Feb. 17, 1916	4 " 10 "	83	Mar. 6, 1916	4 " 30 "
34	Feb. 18, 1916	7 " 00 "	84	Mar. 7, 1916	5 " 05 "
35	Feb. 18, 1916	5 " 05 "	85	Mar. 8, 1916	5 " 20 "
36	Feb. 18, 1916	4 " 50 "	86	Mar. 8, 1916	4 " 40 "
37	Feb. 19, 1916	4 " 30 "	87	Mar. 9, 1916	4 " 50 "
38	Feb. 20, 1916	4 " 45 "	88	Mar. 9, 1916	5 " 40 "
39	Feb. 21, 1916	5 " 40 "	89	Mar. 9, 1916	4 " 10 "
40	Feb. 21, 1916	3 " 55 "	90	Mar. 9, 1916	5 " 00 "
41	Feb. 21, 1916	5 " 00 "	91	Mar. 9, 1916	6 " 25 "
42	Feb. 21, 1916	4 " 15 "	92	Mar. 9, 1916	4 " 10 "
43	Feb. 21, 1916	4 " 50 "	93	Mar. 9, 1916	4 " 55 "
44	Feb. 21, 1916	4 " 30 "	94	Mar. 10, 1916	5 " 05 "
45	Feb. 23, 1916	5 " 40 "	95	Mar. 10, 1916	4 " 50 "
46	Mar. 12, 1916	6 " 10 "	96	Mar. 10, 1916	3 " 55 "
47	Mar. 12, 1916	6 " 30 "	97	Mar. 12, 1916	4 " 45 "
48	Mar. 12, 1916	5 " 05 "	98	Mar. 12, 1916	4 " 55 "
49	Mra. 12, 1916	5 " 40 "	99	Mar. 12, 1916	4 " 25 "
50	Mar. 12, 1916	4 " 50 "	100	Mar. 12, 1916	4 " 10 "

It has been suggested that the thrombokinase which is present in the walls of the bloodvessels may gain access to the circulating

TABLE 3.—COAGULATION TIME TWO HOURS OR MORE AFTER MEALTIME

Observ. No.	Date.	Coagulation time.	Observation No.	Date.	Coagulation time.
1	Mar. 13, 1916	4 min. 55 sec.	51	Mar. 29, 1916	5 min. 10 sec.
2	Mar. 13, 1916	5 " 00 "	52	Mar. 29, 1916	4 " 50 "
3	Mar. 13, 1916	5 " 35 "	53	Mar. 29, 1916	5 " 45 "
4	Mar. 13, 1916	6 " 05 "	54	Mar. 29, 1916	4 " 25 "
5	Mar. 13, 1916	4 " 55 "	55	Mar. 29, 1916	5 " 10 "
6	Mar. 15, 1916	4 " 40 "	56	Mar. 29, 1916	5 " 25 "
7	Mar. 15, 1916	5 " 25 "	57	Mar. 30, 1916	4 " 55 "
8	Mar. 16, 1916.	6 " 10 "	58	Mar. 30, 1916	4 " 40 "
9	Mar. 16, 1916	5 " 15 "	59	Mar. 31, 1916	5 " 50 "
10	Mar. 16, 1916	4 " 55 "	60	Mar. 31, 1916	5 " 05 "
11	Mar. 16, 1916	5 " 35 "	61	Mar. 31, 1916	5 " 10 "
12	Mar. 16, 1916	4 " 40 "	62	Mar. 31, 1916	4 " 55 "
13	Mar. 16, 1916	6 " 15 "	63	April 3, 1916	5 " 15 "
14	Mar. 16, 1916	5 " 20 "	64	April 3, 1916	5 " 00 "
15	Mar. 17, 1916	5 " 05 "	65	April 3, 1916	5 " 50 "
16	Mar. 17, 1916	5 " 30 "	66	April 4, 1916	4 " 30 "
17	Mar. 17, 1916	4 " 40 "	67	April 4, 1916	4 " 50 "
18	Mar. 17, 1916	4 " 55 "	68	April 4, 1916	5 " 35 "
19	Mar. 18, 1916	5 " 40 "	69	April 4, 1916	5 " 20 "
20	Mar. 18, 1916	5 " 15 "	70	April 4, 1916	6 " 20 "
21	Mar. 18, 1916	4 " 50 "	71	April 4, 1916	5 " 30 "
22	Mar. 20, 1916	5 " 10 "	72	April 28, 1916	5 " 50 "
23	Mar. 20, 1916	5 " 25 "	73	April 28, 1916	4 " 50 "
24	Mar. 20, 1916	5 " 10 "	74	April 28, 1916	5 " 25 "
25	Mar. 20, 1916	4 " 35 "	75	April 29, 1916	5 " 10 "
26	Mar. 20, 1916	5 " 50 "	76	April 29, 1916	4 " 35 "
27	Mar. 20, 1916	4 " 50 "	77	April 29, 1916	5 " 20 "
28	Mar. 20, 1916	5 " 30 "	78	April 30, 1916	4 " 55 "
29	Mar. 20, 1916	5 " 00 "	79	April 30, 1916	5 " 50 "
30	Mar. 21, 1916	4 " 55 "	80	May 1, 1916	4 " 30 "
31	Mar. 21, 1916	5 " 30 "	81	May 1, 1916	5 " 05 "
32	Mar. 21, 1916	5 " 10 "	82	May 1, 1916	5 " 20 "
33	Mar. 21, 1916	5 " 45 "	83	May 1, 1916	5 " 00 "
34	Mar. 21, 1916	4 " 35 "	84	May 1, 1916	5 " 35 "
35	Mar. 21, 1916	5 " 20 "	85	May 2, 1916	4 " 50 "
36	Mar. 22, 1916	4 " 40 "	86	May 2, 1916	5 " 10 "
37	Mar. 22, 1916	5 " 10 "	87	May 2, 1916	5 " 40 "
38	Mar. 22, 1916	5 " 15 "	88	May 2, 1916	4 " 45 "
39	Mar. 22, 1916	5 " 10 "	89	May 2, 1916	4 " 55 "
40	Mar. 22, 1916	4 " 55 "	90	May 2, 1916	5 " 20 "
41	Mar. 24, 1916	5 " 20 "	91	May 2, 1916	5 " 00 "
42	Mar. 25, 1916	4 " 30 "	92	May 3, 1916	4 " 50 "
43	Mar. 25, 1916	6 " 20 "	93	May 3, 1916	5 " 05 "
44	Mar. 25, 1916	5 " 20 "	94	May 3, 1916	5 " 10 "
45	Mar. 26, 1916	4 " 35 "	95	May 3, 1916	4 " 35 "
46	Mar. 26, 1916	4 " 50 "	96	May 3, 1916	5 " 25 "
47	Mar. 26, 1916	4 " 40 "	97	May 3, 1916	4 " 50 "
48	Mar. 26, 1916	5 " 05 "	98	May 4, 1916	4 " 55 "
49	Mar. 26, 1916	5 " 11 "	99	May 4, 1916	5 " 10 "
50	Mar. 29, 1916	5 " 30 "	100	May 4, 1916	4 " 40 "

blood owing to an injury of either bacterial or toxic nature of the arterial walls and thus become a factor favoring the process of coagulation. This assumption, however, is not supported by known facts.

Langstern and Mayer[1] contend that the leukocytosis of pneumococcus infections is often attended with a decided increase on fibrinogen held in solution by the plasma. According to Ott,[2] there is a direct relation between the number of leukocytes in the blood and the quantity of fibrinogen.

Mott,[3] Krehl[4] and others hold that a certain parallelism (by no means strict, however,) between the number of leukocytes and the amount of fibrin in the blood exists. Pfeiffer[5] has pointed out that in leukemia the fibrin factors may not be increased at all.

It is to be recollected that fibrinogen is a protein of the globulin class and when it comes into contact with fibrin ferment (resulting from the action of calcium salts upon the thrombogen) either a molecular change takes place in the fibrinogen, or "it is broken up into an unimportant globulin and fibrin" (Hammerstene).[6]

In suppurative processes, however, in which as is well known, leukocytosis occurs, often to a marked degree, the coagulation time is not shortened, hence it may be safely inferred that an increased percentage of white cells contained in the blood alone, is not the sole cause of the abbreviated coagulation time observed in pneumonia. Robertson, Duncan, and Illman[7] were unable to show definite relationship between leukocytosis and coagulation time.

The blood platelets most probably play an unimportant role in the formation of blood-clot. On the other hand, Duke[8] has shown that they have more to do with the retraction of the clot than with its causation.

It is probable that to the disintegration of the white corpuscles

[1] Quoted by Ott, loc. cit.
[2] Text-book of Physiology, 1900, p. 205.
[3] Wien. klin. Wchnschr., 1903, No. 44.
[4] Loc. cit.
[5] Zentralbl. f. inn. Med., 1904, No. 32.
[6] Quoted by Ott, loc. cit.
[7] Jour. Am. Med. Assn., May 16, 1908.
[8] Arch. Int. Med., November 15, 1912, p. 445.

in the drawn blood, fibrinogen (an end-product) owes its origin in a measure at least. May not the extensive destruction of leukocytes in the exudate which occupies the lungs in pneumonia be a factor favoring the coagulative process in this disease? The white corpuscles contain a zymogen, known as prothrombin, which becomes thrombin through the action of calcium salts, hence, it is conceivable that their wide-spread disintegration would liberate sufficient zymogen to hasten the coagulating time in this disease.

Here the question emerges, Since the soluble calcium salts activate the prothrombin in the blood, can the briefer coagulation time of the disease in question be justly attributed to an increased amount of these salts in the blood in pneumococcus infections? In the first place, it is to be noted that the soluble calcium salts are necessary only in the first stage of coagulation, *i. e.*, in the formation of the fibrin-ferment.

It is also well known that a small quantity of the latter substance suffices to activate the fibrinogen, with the production of fibrin. If this be true, then it might be reasonably inferred that different degrees of coaguability of the blood are not dependent to any appreciable extent on the amount of fibrin ferment contained in this tissue.

On the other hand, in diseases in which the coagulation period of the blood is much prolonged, *e. g.*, exophthalmic goitre, calcium salts are among the remedies employed with the object of shortening that period; but experimental investigations leave little doubt that in this manner not much available assistance can be given.

For example, while it has been claimed that the coagulation time has been shortened after the administration of calcium lactate, by certain observers, others, among them Myer Solis-Cohen,[1] contend that the effect of calcium salts in this respect is inconstant. Duncan administered calcium over long periods of time in a series of cases, and was not able to notice any decrease in coagulation time.

Rudolph and Cole[2] after a careful series of studies, came to the conclusion that the "free exhibition of calcium lactate by mouth

[1] Arch. Int. Med., December, 1911. [2] Loc. cit.

has no appreciable effect upon the coagulation of the blood." Again, Van Lier noted the coagulation time in 40 persons before and after the administration of calcium lactate and arrived at the same conclusion.

We tested the blood of 10 healthy persons; the administration of calcium chloride (grs. 10 t. i. d.) for three days was followed by an average shortening of the coagulation time of only 15 seconds. In not a single instance was there more than a feeble effect produced by this calcium salt.

One of us (Meeker) conducted personally a series of chemical investigations into the question of the amount of calcium in the blood during attacks of pneumonia and also in that of healthy individuals, as well as persons suffering from other complaints, for purposes of comparison. The results obtained are indicated clearly in the accompanying tables (Nos. 4 and 5); they show a striking similarity to one another, hence it may be claimed that the calcium content of the blood does not, according to these observations at least, exceed the normal amount in pneumonia. That the results of these experiments, however, need confirmation is freely admitted.

TABLE 4.—CALCIUM, MAGNESIUM, AND IRON IN HUMAN BLOOD CALCULATED AS CaO, MgO, and Fe. RESULTS IN PERCENTAGES. NORMAL.[1]

Mark.	Sex.	Age.	Diagnosis.	Blood, grams.	CaO.	MgO.	Fe.
Dr. B. . . .	..	24	Well	19.9202	.0084		
Dr. T. . . .	..	27	Well	10.2904	.0077		
UM., 2 . . .	..	25	Primary	35.4651	.0072	.0045	.0345
UM., 3 . . .	..	32	Latent	36.2199	.0062	.0063	.0518
UM., 4 . . .	..	21	Tertiary	29.9138	.0077	.0065	.0459
UM., 5 . . .	..	24	Secondary	32.5327	.0065	.0071	.0508
UM., 6 . . .	..	24	Herpes	36.6707	.0073	.0065	.0489
Average . .	..	..	...	....	.0073	.0062	.0564

From the above studies, we may draw the following tentative inferences:

1. The coagulation time is somewhat shortened in lobar pneumonia.

[1] From well persons and luetics in good general health. Right median venipuncture.

TABLE 5.—CALCIUM, MAGNESIUM, AND IRON IN HUMAN BLOOD CALCULATED AS CaO, MgO, AND Fe. RESULTS IN PERCENTAGES. PNEUMONIAS.[1]

Mark.	Sex.	Age.	Diagnosis.	Blood, grams.	CaO.	MgO.	Fe.	Date.
H. D., 1	M.	67	Pneumonia	19.2070	.0070	.0069	.0423	Mar. 9, 1916
H. D., 2	M.	67	Pneumonia	45.4000	.0074	.0065	.0428	Mar. 18, 1916
G. B., 1	F.	35	Pneumonia	42.7685	.0064	.0070	.0380	Mar. 14, 1916
G. B., 2a	F.	35	Pneumonia	48.5300	.0078	.0074	.0398	April 9, 1916
G. B., 2b	F.	35	Pneumonia	43.6430	.0082	.0078	.0424	April 9, 1916
T. H., 1	M.	17	Pneumonia	13.8590	.0087	.0067	.0222	Mar. 15, 1916
T. H., 2	M.	17	Pneumonia	38.4619	.0086	.0061	.0263	Mar. 16, 1916
T. H., 3	M.	17	Pneumonia	39.7680				
J. L.	M.	20	Pneumonia	29.2625		Combined		April 5, 1916
TH3 JL.	M.	..	Pneumonia	..	.0075			
L. R.	M.	19	Pneumonia	51.5600	.0082	..	.0429	Mar. 21, 1916
W. S., 1	M.	20	Pneumonia	20.8785	.0074	.0077	.0510	April 2, 1916
W. S., 2	M.	..	Pneumonia	25.2500	.0077	.0079	.0455	April 4, 1916
Average	..	..	...	..	.0071	.0071	.0393	

2. The cause or causes of this abbreviation are not definitely known.

3. The influence of a meal on the coagulation time is trivial, but practically constant.

4. The effect of the administration of calcium salts upon the coagulative process must be quite inconsiderable.

5. The calcium present in the blood in lobar pneumonia does not exceed the normal amount.

We desire to express our cordial thanks to Dr. H. Leon Jameson and Dr. J. W. Troxell, for much assistance in carrying out the tests for determining the coagulation time.

DISCUSSION

DR. RUFUS I. COLE, New York, called attention to Dochez's work in which it was found that in blood obtained direct from the vein in pneumonia the fibrinogen is increased, but the coagulation time is prolonged.

[1] These were from cases of pneumonia in the Medico-Chirurgical Hospital. Mainly median venisections.

Dr. Henry Sewall, Denver, said the profession does not yet realize the truth of Dochez's observation: that there is more fibrinogen, but longer coagulation time in pneumonia.

Dr. Max Einhorn, New York, asked if the retention of NaCl in the blood in pneumonia may not play a part in accelerating the coagulation time.

Dr. S. J. Meltzer, New York, said that in experimental pneumonia they found that when produced by non-virulent organisms there was very little increase in the fibrin content of the exudate. The increase of this element, however, was considerable in experiments with virulent organisms. Starch pneumonia is not attended with fibrin increase.

Dr. J. M. Anders, Philadelphia, said with reference to Dr. Cole's remarks, he had felt that in pneumonia we have a paradox in the behavior of the blood: in the course of the disease there is a shortened coagulation time; but clots found postmortem show a buffy coat, as a rule, indicating that their formation was slow and during life. Venipuncture may prevent the body fluids from influencing the results; he hoped to do further work on that basis.

EXPERIMENTS WITH POLIOMYELITIS IN THE RABBIT

By M. J. ROSENAU, M.D.

AND

L. C. HAVENS

BOSTON, MASSACHUSETTS

Inoculation of the common laboratory animals with the virus of poliomyelitis has met with so little success that the disease has been generally regarded as exclusively limited to man and the monkey. Attempts have been made to transmit the virus to many animals, but of all the animals tested, positive results have thus far been recorded only for monkeys, rabbits, and, perhaps, guinea-pigs.

Krause and Meinicke[1] reported the passage of a strain of virus obtained from a human case through seven generations in rabbits. Lentz and Huntemüller[2] report having successfully transferred the virus from rabbit to rabbit by various methods of inoculation. They found the alterations in the brain and spinal cord to be slight as compared with those in monkeys. On the other hand, Römer and Joseph,[3] Landsteiner and Levaditi,[4] Leiner and von Wiesner,[5] and Flexner and Lewis[6] all failed to transfer the disease to rabbits. The most striking results, perhaps, have been reported by Marks,[7] who carried a strain of poliomyelitic virus derived from a *rhesus* monkey through seven generations of young rabbits varying in weight from 350 to 550 gm. The animals that succumbed developed

[1] Deutsch. med. Wchnschr., 1909, xxxv, 1825.
[2] Ztschr. f. Hyg. u. Infectionskrankh., 1910, lxvi, 481.
[3] München. med. Wchnschr., 1910, lvii, 2685.
[4] Compt. rend. Soc. de biol., 1909, lxvii, 787.
[5] Wien. klin. Wchnschr., 1909, xxii, 1698.
[6] Jour. Exper. Med., 1910, xii, 227.
[7] Ibid., 1911, xiv, 116.

no paralysis, but died in convulsions. No lesions definitely characteristic of poliomyelitis could be found on microscopic examination. Marks says: "The disease thus produced in rabbits cannot be recognized as poliomyelitis," although he concludes that filtrates of the nervous tissues of monkeys dying from experimental poliomyelitis are not wholly innocuous to young rabbits. Marks further states that "not all strains of the virus can be transmitted successfully to even a small fraction of individuals of all varieties of domesticated rabbits." This fact, which we have corroborated, may explain the negative results of other investigators.

Römer and Joseph[1] have observed that guinea-pigs in the laboratory occasionally die of a paralytic disease. They were unable to transfer poliomyelitic virus from monkeys to guinea-pigs, although Römer[2] found that the spontaneous paralysis was due to a filterable virus. Neustaedter[3] claims to have carried a strain from a guinea-pig presumably infected through contact with a monkey into one other guinea-pig and back again to a monkey.

In the course of our experiments we have inoculated a few guinea-pigs. The lesions in those that succumbed were somewhat similar to the lesions seen in the rabbits. This part of our work is not sufficiently advanced to warrant conclusions. Moreover, we have no criterion by which to establish what is and what is not poliomyelitis, except by reproducing the disease in monkeys. It is therefore hazardous to affirm or deny the identity with poliomyelitis of these aberrant conditions in other animal species.

The difficulty of obtaining monkeys on account of the war led us to consider other animals that might be susceptible and therefore suitable for experimental purposes. We selected the rabbit because successful results had previously been obtained with these rodents and because rabbits offered a good chance to compare the action of poliomyelitic with rabic virus. We accordingly inoculated rabbits with poliomyelitic virus from a *rhesus* monkey infected by intracranial inoculation with a strain sent us from the Rockefeller Institute for Medical Research by Dr. Harold L. Amoss. We have

[1] Loc. cit.
[2] Ergebn. d. inn. Med. u. Kinderh., 1912, viii, 1.
[3] Jour. Am. Med. Assn., 1913, lx, 982.

obtained positive results in young rabbits and have succeeded in transferring the virus from rabbit to rabbit through eight successive generations.

Intracranial inoculations have been used for the most part, although infection has taken place through intravenous injection, also through injection into the sciatic nerve sheath, and even after introduction of the virus into the anterior nares, upon the uninjured nasal mucosa. A few intraperitoneal injections were tried, but with negative results.

All inoculations are by no means successful. Over one-half fail; we obtained positive results in twenty-two rabbits out of a total of fifty-four inoculated in various ways. Of five rabbits inoculated with the virus from the *rhesus* monkey two have failed to show symptoms, although kept under observation for five months.

The age incidence of poliomyelitis in man is indicated by the name "infantile paralysis." In our experimental work we obtained positive results in young rabbits only. We failed to infect three full-grown rabbits with *rhesus* virus, although this same virus caught in three out of five young rabbits. Furthermore, rabbit virus from the second and third generations was transferred to rabbits eight weeks old with negative results. Thereafter we used only young animals under six weeks old in our experiments. There seems to be a parallel between rabbits and man as far as susceptibility of the young is concerned. These facts seem to furnish a striking example of natural immunity acquired during the period of adolescence.

The incubation period in our observations of twenty-two rabbits has been variable, the shortest being two days, the longest, forty-one. In this respect our experience is similar to that of Lentz and Huntemüller,[1] who found the incubation period to be of uncertain length, sometimes as long as two months, but usually between seven and eleven days. The average period of incubation in our observations was twelve days. Curiously enough, the shortest period, two days, as well as the longest, forty-one days, was after intracranial injections.

The virus so far has given no evidence of increasing adaptation to

[1] Loc. cit.

rabbits, or of becoming fixed to any degree, the number of failures being as great, and the period of incubation as variable, in the eighth generation as in the first.

The symptoms also vary. They can, however, be divided roughly into two classes: (1) A type which we designate the progressive type, in which the rabbit first becomes inactive, loses weight, and appears weak. This is followed by partial or complete paralysis of one or more of the extremities, which usually progresses until death. This corresponds somewhat to the syndrome most commonly seen in experimental poliomyelitis in monkeys. The duration of the disease varies from one or two days to one week. The paralysis is usually flaccid, but occasionally it is spastic. Sometimes the paralysis begins locally. As a rule it is easy to determine that the paralysis is a true palsy and not simply "weakness." (2) The other group of symptoms, which we designate the fulminating type, is more explosive in character, develops suddenly, and terminates in a very short time; it never extends over more than two days and usually lasts only a few hours. The overshadowing symptoms are extreme weakness and marked dyspnea. As an illustration of the rapid course of the symptoms of the fulminating type the case of Rabbit 21 is cited. This rabbit was inoculated intravenously on August 18 with 1 c.c. of a rich emulsion of virus from a first generation rabbit (No. 34). On September 12, twenty-five days later, it still appeared to be normal. In about an hour after this observation it was found by one of us lying flat on its side, breathing in slow, labored gasps. There was great general weakness, the rabbit being unable to raise its head, but no paralysis of the extremities was demonstrable. Within a few minutes the animal was dead, the whole syndrome lasting less than an hour. This is an extreme instance of the fulminating type, and is of special interest since it follows a long period of incubation. We have seen combinations of the two types with symptoms resembling Landry's paralysis.

Most of the animals in which the symptoms lasted over two or three days lost weight rapidly. In some cases the loss of weight was the first observed symptom.

That the rabbit virus is filterable is shown by the protocol of Rabbit 13 of the second generation. This rabbit was inoculated

intracranially with 0.5 c.c. of a Berkefeld filtrate of brain and cord emulsion from Rabbit 10. Six days later the hind legs became paralyzed, and the animal died two days after onset with symptoms of the fulminating type. The unfiltered virus from Rabbit 13 proved infectious for two other rabbits (Nos. 20 and 23).

We have inoculated a monkey with virus from Rabbit 49 of the seventh generation. The monkey died after an incubation period of four weeks, with symptoms somewhat resembling the fulminating type seen in the rabbits. The gross pathological findings were congestion of the pia, especially in the region of the medulla, and hyperemia and hemorrhage of the gray matter of the medulla and cord. The microscopic lesions were similar to those seen in the rabbits and not typical of experimental poliomyelitis in monkeys. The monkey was a South American species which we have since found to be highly resistant to poliomyelitic virus derived from *rhesus* monkeys. This interesting observation is being made the subject of further study.

Flexner found that *Capucinus* monkeys were resistant, although *Cebus*, another South American species, were susceptible, but less so than Old World monkeys. He therefore concludes that the *Platyrrhines* are less susceptible than the *Catarrhines*.[1]

The intracranial inoculations were done by making a small incision in the skin, near the midline, drawing this to one side, and introducing the needle of the syringe directly through the frontal bone, which is thin and soft in young rabbits. The virus is then injected slowly into the region of the lateral ventricle. On withdrawing the needle, the skin slides back and acts as a valve to cover the small opening in the bone.

The emulsion of virus in all cases was made by grinding in a mortar, portions of the brain and cord with salt solution, and filtering through several layers of sterile gauze.

In Table I are briefly summarized the results of the rabbits which succumbed to intracranial inoculation.

Fourteen rabbits inoculated intracranially failed to show symptoms.

[1] Jour. Am. Med. Assn., 1910, lv, 1105.

The intravenous inoculations were made into the posterior auricular vein with an emulsion of the central nervous matter prepared as above described.

Table II contains a condensed summary of the rabbits which succumbed to intravenous inoculations.

Six rabbits inoculated intravenously failed to show symptoms.

In order to inject the virus into the sciatic nerve sheath, a short incision was made in the skin above the nerve, the tissues were dissected sufficiently to render the nerve visible, and the needle was then inserted into the sheath in the central direction. The emulsion was prepared as above.

Table III gives a condensed summary of the rabbits which succumbed as a result of injection into the sciatic nerve sheath.

Five rabbits inoculated into the sciatic nerve sheath failed to develop symptoms.

TABLE I.—INTRACRANIAL INOCULATION

No. of rabbit.	Amount of emulsion. C.c.	Rabbit generation.	Period of incubation. Days.	Type of symptoms.[1]
19	0.5	I	19	P.
35	0.5	II	5	P.
27	0.25	II	31	F.
28	0.25	II	34	F.
13	0.5	II	6	F.
20	0.5	III	41	F.
23	0.5	III	9	P.
22	0.8	III	10	P.
46	0.25	III	10	Convulsions.
15	0.5	III	2	F.
9	0.5	III	14	P.
16	0.5	IV	13	P.
41	0.5	V	12	P.

TABLE II.—INTRAVENOUS INOCULATION

No. of rabbit.	Amount of emulsion. C.c.	Rabbit generation.	Period of incubation. Days.	Type of symptoms.
34	1.0	I	18	F.
10	1.0	I	3	F.
21	1.0	II	25	F.

TABLE III.—INOCULATION INTO THE SCIATIC NERVE SHEATH

No. of rabbit.	Amount of emulsion. C.c.	Rabbit generation.	Period of incubation. Days.	Type of symptoms.
43	0.5	VI	8	P.
49	0.5	VII	6	F.
61	1.0	VIII	20	F.

[1] In this and the following tables the letter P indicates symptoms of the progressive type; F, symptoms of the fulminating type.

In order to introduce the virus into the nose, the following procedure was adopted: The rabbit was lightly etherized, held on its back, and the emulsion of the virus then dropped into the anterior nares from an ordinary medicine dropper, care being taken not to injure the mucosa. There was usually a little sneezing immediately after the fluid was introduced.

Table IV is a condensed summary of the three rabbits which succumbed as a result of intranasal insufflation.

TABLE IV.—INTRANASAL INSUFFLATION

No. of rabbit.	Amount of emulsion. C.c.	Rabbit generation.	Period of incubation. Days.	Type of symptoms.
33	0.5	VI	2	F.
36	0.5	V	2	F.
64	0.25	VIII	2	F.

Six rabbits inoculated by intranasal insufflation failed to develop symptoms.

It will be seen that, judging from the limited data at hand, this is a particularly virulent way of infecting rabbits with the virus. The period of incubation is short—only two days—and the symptoms in all three cases were of the fulminating type. These represent only three out of nine rabbits tested by introducing the virus into the nose. The other six failed to take. Particular attention was paid to the lungs of the rabbits in this group at autopsy. There was no evidence of pneumonia, or even of congestion of the lungs. On microscopic examination it was found that the medulla was markedly congested, whereas the cord was only slightly affected.

The gross lesions consist of injection of the vessels of the pia, hyperemia of the gray matter of the medulla and cord, and more or less marked edema throughout the brain and cord. The microscopic lesions are distributed rather uniformly throughout the gray matter of the cord and medulla in the progressive type. In the fulminating group (those exhibiting symptoms of respiratory failure without paralysis of the skeletal muscles), the lesions are more marked in the medulla. The microscopic lesions consist of capillary congestion, focal hemorrhages into the gray matter, degeneration of the large motor cells, and infiltration with cells of uncertain origin. These cells for the most part seem to be proliferated glia

cells, and therefore appear to be different from the infiltrating lymphocytes of the lesions of poliomyelitis in man. The congestion of the capillaries and small arterioles is conspicuous. The infiltrating cells when stained with eosin and methylene blue have large, vesicular nuclei with a number of conspicuous chromatin granules. The cytoplasm is scanty and homogeneous. They are scattered throughout the gray matter, and are also grouped in satellite arrangement around the nerve cells, but the perivascular infiltration, so typical of the lesions of poliomyelitis in man and the monkey, is absent in the rabbit. Punctate hemorrhages are numerous, sometimes every vessel in a field being ruptured. The nerve cells show all stages of degeneration. Chromatolysis is common and satellitosis is an almost constant feature. A moderate degree of round-cell infiltration is occasionally seen in the meninges. The accompanying plates illustrate the different features of the lesions. The complete picture gives the impression of a severe intoxication of the gray matter of the cord and medulla.

The following are the protocols in brief of the rabbits that succumbed, arranged chronologically.

Rabbit 34.—Age 6 weeks. Weight 660 gm. 1st generation. 1 c.c. of *rhesus* virus intravenously. Incubation period 18 days. Died in the night with no observed symptoms.

Rabbit 19.—Age 5 weeks. Weight 600 gm. 1st generation. 0.5 c.c. of *rhesus* virus intracranially. Incubation period 19 days. Death in 4 days. Paralysis of front legs with respiratory symptoms.

Rabbit 10.—Age 4 weeks. Weight 550 gm. 1st generation. 1 c.c. of *rhesus* virus intravenously. Incubation period 3 days. Died in the night with no observed symptoms.

Rabbit 21.—Age 5 weeks. Weight 600 gm. 2d generation. 1 c.c. of virus of Rabbit 34 intravenously. Incubation period 25 days. Death in 1 hour. Symptoms very explosive in character; complete prostration and marked dyspnea.

Rabbit 35.—Age 6 weeks. Weight 730 gm. 2d generation. 0.5 c.c. of virus of Rabbit 34 intracranially. Incubation period 5 days. Hind legs became paralyzed. Paralysis remained stationary for 5 days, then showed tendency to improvement. Chloroformed.

Rabbit 27.—Age 3 weeks. Weight 290 gm. 2d generation. 0.25 c.c. of virus of Rabbit 34 intracranially. Incubation period 31 days. Death in 1 day. Paralysis and dyspnea.

Rabbit 28.—Age 3 weeks. Weight 255 gm. 2d generation. 0.25 c.c. of virus of Rabbit 34 intracranially. Incubation period 34 days. Death in 1 day. Weakness and dyspnea.

Rabbit 13.—Age 4 weeks. Weight 540 gm. 2d generation. 0.5 c.c. of Berkefeld filtrate of emulsion of virus of Rabbit 10 intracranially. Incubation period 6 days. Death in 2 days. Paralysis of hind legs and respiratory distress.

Rabbit 20.—Age 5 weeks. Weight 645 gm. 3d generation. 0.5 c.c. of virus of Rabbit 13 intracranially. Incubation period 41 days. Death in 1 day. Explosive symptoms; prostration and marked dyspnea.

Rabbit 23.—Age 4 weeks. Weight 410 gm. 3d generation. 0.5 c.c. of virus of Rabbit 13 intracranially. Incubation period 9 days. Death in 5 days. General weakness and dyspnea.

Rabbit 22.—Age 5 weeks. Weight 620 gm. 3d generation. 0.8 c.c. of virus of Rabbit 21 intracranially. Incubation period 10 days. Death in 7 days. Paralysis progressive.

Rabbit 46.—Age 5 weeks. Weight 380 gm. 3d generation. 0.25 c.c. of virus of Rabbit 27 intracranially. Incubation period 10 days. Death in 1 day. Died in convulsions.

Rabbit 15.—Age 6 weeks. Weight 520 gm. 3d generation. 0.5 c.c. of virus of Rabbit 35 intracranially. Incubation period 2 days. Symptoms progressed rapidly; respiratory distress and great weakness. Chloroformed.

Rabbit 9.—Age 4 weeks. Weight 440 gm. 3d generation. 0.5 c.c. of virus of Rabbit 35 intracranially. Incubation period 14 days. Death in 7 days. Progressive paralysis with respiratory distress.

Rabbit 16.—Age 4 weeks. Weight 430 gm. 4th generation. 0.5 c.c. of virus of Rabbit 15 intracranially. Incubation period 13 days. Death in 8 days. Symptoms progressive in type with dyspnea.

Rabbit 33.—Age 6 weeks. Weight 620 gm. 4th generation. 0.5 c.c. of emulsion of virus of Rabbit 9, half the amount dropped in each nostril. Incubation period 2 days. Death in 1 day. Symptoms of the fulminating type with paralysis of hind legs toward the last.

Rabbit 41.—Age 5 weeks. Weight 560 gm. 5th generation. 0.5 c.c. of emulsion of virus of Rabbit 33 intracranially. Incubation period 12 days. Death in 4 days. Symptoms of progressive type.

Rabbit 36.—Age 4 weeks. Weight 380 gm. 5th generation. 0.25 c.c. of heavy emulsion of virus of Rabbit 33 in each nostril. Incubation period 2 days. Death in 2 days. Symptoms of fulminating type with paralysis.

Rabbit 43.—Age 5 weeks. Weight 450 gm. 6th generation. 0.5 c.c. of emulsion of virus of Rabbit 36 injected into sciatic nerve sheath. Incubation period 8 days. Symptoms progressive in type. Complete paralysis on 3d day. Chloroformed.

Rabbit 49.—Age 4 weeks. Weight 310 gm. 7th generation. 0.5 c.c. of emulsion of virus of Rabbit 43 into sciatic nerve sheath. Incubation period 6 days. Death in 2 days. Symptoms fulminating in type.

Rabbit 64.—Age 4 weeks. Weight 400 gm. 8th generation. 0.25 c.c. of emulsion of virus of Rabbit 49 into each nostril. Incubation period 2 days. Death in 2 days. Symptoms of fulminating type.

Rabbit 61.—Age 4 weeks. Weight 340 gm. 8th generation. 1 c.c. of emulsion of virus of Rabbit 49 into sciatic nerve sheath. Incubation period 20 days. Died in night with no observed symptoms.

Discussion and Summary. The poliomyelitic virus obtained from an experimental monkey has been passed through eight generations in rabbits. It shows no signs of dying out. On the other hand, it gives no evidence of becoming more pathogenic to the species through successive passage. The period of incubation remains variable and the percentage of "takes" has not increased. Whether eventually a virus can be obtained which is of heightened virulence to rabbits is problematic.

All inoculations are by no means successful. The animals show great individual differences in susceptibility to the virus, as is evidenced by the fact that out of fifty-four rabbits inoculated, only twenty-two, or about 40 per cent., succumbed. This fact may explain the negative results of other investigators. At several points in the series of experiments it was thought that the strain had died out. As many as six rabbits have been inoculated, one after the other, before the virus would catch again.

The age of the rabbits is important in considering the susceptibility. From the limited data at our command, adult rabbits are resistant, and there appears to be an abrupt increase in resistance between the age of six and eight weeks; that is, rabbits under six weeks are more susceptible to the virus. There seems to be a parallel between the age incidence of this disease in rabbits and spontaneous poliomyelitis in man. The age incidence of poliomyelitis in man is indicated by the term "infantile paralysis."

Several methods of inoculation have proved successful; thus the rabbits have succumbed as a result of introducing the virus directly into the brain, by injecting it into a peripheral nerve, or directly into the circulation, or by placing it upon the uninjured nasal mucosa.

The symptoms produced show more or less departure from the

symptoms of poliomyelitis as seen in the spontaneous disease in man and in the experimental disease in the monkey. There are two distinct pictures recognizable. In one there is paralysis of one or more of the extremities which progresses until death, resembling somewhat the symptoms of the experimental disease in the monkey. This we have designated the progressive type. The other group is included in what we have called the fulminating type. The symptoms are explosive in character, with extreme weakness amounting to prostration, terminating in death in a few hours, attendant upon respiratory failure. The mode of inoculation seems to have little effect upon the type of symptoms produced.

The period of incubation is variable and apparently does not depend upon the method of inoculation. The period varied from two to forty-one days, with an average of twelve days. The two extremes both occurred after intracranial injection. After intranasal insufflation the incubation period was short, being in each case two days, followed by symptoms of the fulminating type. The placing of the virus into the nose seems to be an effective method, but is as uncertain as other routes, as only three out of nine rabbits tested in this manner succumbed. The disease produced by this route was particularly virulent.

The virus shows no tendency to become fixed. The period of incubation is as variable in the eighth generation as in the first, and the virus has shown no tendency toward increasing virulence through successive passage, in these respects differing from the virus of rabies.

We have found the virus to be filterable. An emulsion of the central nervous matter of a rabbit of the first generation passed through a Berkefeld filter, and injected intracerebrally into another rabbit, resulted in death, preceded by symptoms of the fulminating type. Virus (unfiltered) from this rabbit was transferred successfully to two other rabbits.

The lesions, while definite and consistent throughout the series, lack the distinctive features of the pathological picture of poliomyelitis in man and the monkey. Capillary congestion, punctate hemorrhages, degeneration of the motor cells, satellitosis, and more or less cellular infiltration of the gray matter of the cord and medulla

are found, but perivascular infiltration is absent and the infiltrating cells are not lymphocytic in character.

One of the most striking features of this investigation is the way in which rabbits and monkeys react to the same virus. The disease in the rabbit presents certain clinical resemblances to the experimental disease in the monkey and also to the spontaneous disease in children. On the other hand, the symptoms show marked variation from those seen in the monkey and in man. The picture has not the same constancy in rabbits and could not in most cases be recognized clinically as poliomyelitis. There are still more marked differences in the pathology. While it is true that the brunt of the attack in the rabbit falls upon the gray matter of the cord and medulla, the appearance of the lesions under the microscope shows such differences from the lesions of experimental poliomyelitis in monkeys, as well as the natural disease in man, as to suggest two distinct infections. It is more reasonable, however, to assume that we are dealing with a modified form of poliomyelitis; that the rabbit reacts differently to the virus than the monkey or man; and that the disease produced in rabbits by us and others is in fact poliomyelitis. So far as we know, no other virus produces such differences in two animal species. Smallpox is so profoundly altered in the cow that it took almost one hundred years to prove Jenner's assumption that cow-pox is a modified form of smallpox. However, the pock of vaccinia is a correct counterpart, both clinically and pathologically, of the pock of variola. If the virus of poliomyelitis may be so altered in the rabbit as scarcely to be recognizable, may it not be still more profoundly changed in other animals? The conjecture then arises that poliomyelitis, instead of being limited naturally to man and experimentally to monkeys, may in fact occur in other animals in unnoticed or unrecognized form. If this should prove true, it may be a source of human infection and may help to solve the problem of prevention.

GASTROHYDRORRHEA IN CIRRHOSIS OF THE LIVER ACCOMPANIED BY PYLORIC STENOSIS

By MAX EINHORN, M.D.
NEW YORK

By the term "gastrohydrorrhea" is meant the flow of a watery fluid from the stomach, containing neither hydrochloric acid nor the characteristic ferments.

I may be permitted to describe the case in which gastrohydrorrhea was most marked and first noticed.

Antonio C., about forty-two years old, consulted me August 31, 1915, for the first time. He then complained of vomiting small quantities of fluid, principally in the morning, anorexia, slight constipation, and great loss in weight, during the last six months about fifty pounds. He used to consume great quantities of alcoholic beverages, and had syphilis twenty years ago. The examination showed no abnormalities in the chest. The abdomen, likewise, failed to reveal any gross pathological changes. The stomach extended to the navel. The liver was not palpable. The urine contained no albumin nor sugar, but a considerable quantity of urobilinogen.

Based upon the symptoms and etiology, a tentative diagnosis of gastric catarrh (due to the abuse of alcohol) and beginning cirrhosis of the liver was made.

Patient was instructed not to partake of any alcoholic beverages, and to eat plain foods, avoiding much meat and highly seasoned substances. He was also given—

Extr. fluid condurango,
Extr. fluid quassiæ,
Extr. fluid cascar. sagr. āā 10.0.
M. Sig.—20 drops t. i. d.

Patient (who lived in a distant country) then improved for quite a while (during the whole month of October, eating with impunity, without vomiting), when suddenly the old symptoms returned with greater severity.

At the beginning of November he was seized with incessant vomiting. The attending physician instituted rectal feeding for about two weeks, but even then the vomiting persisted. Patient was then brought to the German Hospital and placed under my care.

November 15, 1915. Patient is extremely emaciated and weak; he can hardly talk. His tongue is dry and reddish. Heart sounds are very weak, but no murmur is present.

The stomach is somewhat dilated, extending to one finger's breadth below the navel, and somewhat painful to pressure. No resistant mass can be discovered. Liver dulness is slightly diminished, extending merely to one inch above the right costal margin. The vomited matter contains no hydrochloric acid and is of a neutral reaction; blood is present, but no Oppler-Boas bacilli. Rennet is absent. The urine, spec. gravity 1010, contains no albumin nor sugar but a great quantity of acetone.

On November 16 the stomach is emptied in the fasting condition, 75 c.c. being obtained; fluid looks dark brown, containing a large quantity of mucus: HCl = 0; acidity = 18; lactic acid + trace; blood +; large amount of bacteria, mostly cocci; no sarcinæ.

The duodenal bucket, given with atropin, did not pass the pylorus. Stool not formed, dark brown, contains a considerable quantity of mucus; occult blood present.

Blood—hemoglobin, 80 per cent.
Red blood corpuscles, 5,000,000.
White blood corpuscles, 12,600.
Polynuclears, 77 per cent.
Lymphocytes, 21 per cent.
Transitional, 1 per cent.
Eosinophiles, 1 per cent.

Patient complains of great weakness and vomits almost constantly. The diagnosis at present appeared to be severe gastritis with multiple erosions, stricture of the pylorus (with the possibility of malignancy), and cirrhosis of the liver. The patient was given—

℞—Menthol, 1.0.
Spirit. vin., 50.0.
Aq. dest., 120.0.
Syr. zingib., 30.0.
M. Sig.—One tablespoonful, t. i. d.

and placed on the following régime: one ounce of either barley water or egg albumen water, alternating every hour by mouth; 1,000 c.c. glucose solution 6 per cent. by the Murphy drip per rectum twice daily; gastric lavage every morning in the fasting condition. Under this régime the urine increased and the tongue became moist. Patient felt somewhat easier;

but the vomiting persisted. The quantity vomited always exceeded by far the ingested amount of fluid. Thus on the 19th of November the intake per os amounted to 540 c.c., while the quantity vomited was 1,310 c.c. In this vomited material there was no trace of gastric juice (reaction neutral or rather slightly alkaline), nor was there bile nor pancreatic juice. It always contained some blood and mucus, the blood at times macroscopically visible, at times found merely by chemical tests. Although a Wassermann test was negative, we decided to apply antisyphilitic treatment. Mercury salicylate was given subcutaneously, and potassium iodide per rectum.

Nutritive enemas were added to the glucose solution and for a time nothing was given by mouth for twenty-four hours, but the vomiting persisted, 1,500 c.c. being collected during that period. Patient gradually grew weaker, and notwithstanding gastric lavage and total abstinence of fluids by mouth, kept on vomiting $1\frac{1}{2}$ to 2 quarts daily of a watery mucous fluid, at times tinged with blood. November 24 the patient became irrational and also developed a slight rise in temperature. On November 25 he lost consciousness and died on November 27, without any additional new symptoms.

The autopsy was performed in my presence about five hours after the exitus by Dr. Humphreys, the pathologist of the German Hospital, whose report I herewith submit.

"Anatomical Diagnosis: Carcinoma of the pylorus and stomach; dilatation of the stomach; chronic passive congestion; atrophic cirrhosis of the liver; lobar pneumonia. Body is that of an elderly man of large frame but much emaciated. The skin is pale and of a subicteroid tint. Rigor mortis is present. Postmortem lividity slight. Marked emaciation of face, trunk and limbs. One lymph node is palpable in the neck about the size of a hazel-nut.

"*Diaphragm.* Fourth rib right side, fourth interspace left side.

"*Peritoneal Cavity.* The intestines are moderately ballooned with gas. The stomach is very markedly ballooned, crowding over beyond the line of the gall-bladder. The serous surfaces are smooth and glistening throughout. The lesser omentum is shortened and thickened, and adherent to the pylorus. The bladder is distended with dark urine. The mesentery fat is slight in amount but not absent. On the surface of the mesentery are found numerous small reddened areas resembling petechia. The free border of the lumen is entirely invisible behind the border of the ribs.

"*Pleura.* Left pleura normal. Right pleura shows old adhesions posteriorly.

"*Pericardium.* Normal.

"*Heart.* Normal in general size and appearance. The valves and orifices are normal. Myocardium slightly pale, shows no areas of degeneration or fibrosis.

"*Lungs.* Both lungs show marked hypostatic congestion of the lower lobe. On the left side are found numerous small areas of consolidation of very recent origin, poorly marked off from the surrounding tissues as dark red spots. The lower lobes of both sides are edematous but show no pneumonia.

"The bronchi are moderately congested.

"*Spleen.* Somewhat enlarged, measuring 12 by 7 by 4 cm. It is rather firm but friable in consistence. The capsule shows one or two areas of local thickening. The pulp is of a deep purplish-red color, appears swollen. The stroma is still visible. Malpighian bodies are invisible.

"*Liver.* Much diminished in size, weighs 1,600 grams. The surface is coarsely granular and of a pale yellowish-brown color. It cuts with resistance. The cut surface appears of a yellowish-brown color, subdivided by fibrous tissue trabeculæ into islands 3 or 4 mm. in diameter. The normal markings are completely obliterated. The gall-bladder appears normal excepting for adhesions on its outer surface; contains a small quantity of thick bile.

"*Kidneys.* About normal in size and consistence; their capsules strip readily, leaving a smooth, rather deep red surface. On the left kidney near the hilus is a small cyst about 1.5 cm. in diameter filled with clear yellow fluid. On section the cortex appears moderately congested, slightly thickened but otherwise normal. The pelvis and ureters appear normal. The bladder shows one or two pectechia on its surface but otherwise is normal.

"*Pancreas.* Somewhat small and firm but on section appears normal.

"*Gastro-intestinal Canal.* Esophagus normal. Stomach immensely ballooned with gas, contains a small quantity of brownish fluid. At the pylorus is felt a hard tumor which apparently encircles the lumen. It measures about 3 cm. in all dimensions. The blade of a scissors can be run throughout it from the duodenum into the cavity of the stomach. On opening the organ the mucous membrane throughout the whole stomach is of a deep purplish-red color. At the pylorus the wall is thickened, measuring about 1.5 cm. through. The mucosa at this point is ulcerated and eroded, but the floor of the ulceration appears clean. No metastases were found in the lymph nodes in the lesser or greater omentum. The duodenum is intensely congested similarly to the stomach. The small intestine less so. The large intestine is very markedly congested in the lower portion. Nowhere is there any ulceration. The aorta is rather narrow, shows a few deep atheromatous patches in its first portion. The abdominal portion appears normal."

A section of the pyloric tumor was submitted to Dr. James Ewing, who was kind enough to examine it. He reports as follows:

January 14, 1916. "Report on Fibrocarcinoma of Pylorus. The pyloric muscle is infiltrated with somewhat indefinite cells which form an anastomos-

ing network, dividing up the muscle bundles into large groups. The infiltration is exclusively through the connective tissue. The subserous fat

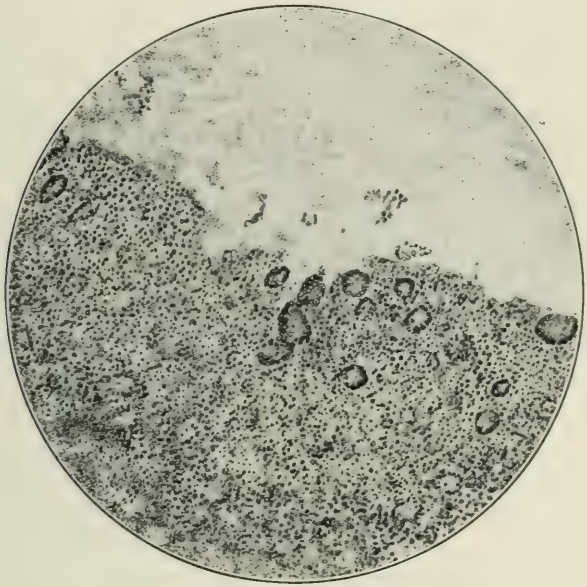

FIG. 1.—Section through the gastric mucosa. The glands are destroyed to a great extent. Numerous infiltrating cells are noticeable, also, at places; surface defects of the mucosa. (Small magnification.)

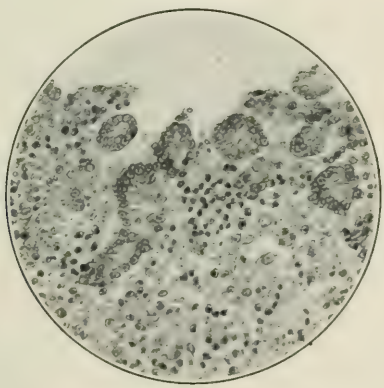

FIG. 2.—The same as Fig. 1 under higher magnification.

tissue is also the seat of small groups of hyperchromatic cells of indefinite type. The mucosa is missing and there is little submucous tissue present.

On careful inspection the infiltrating cells prove to be typical of gastric fibrocarcinoma. They are small polyhedral with compact hyperchromatic

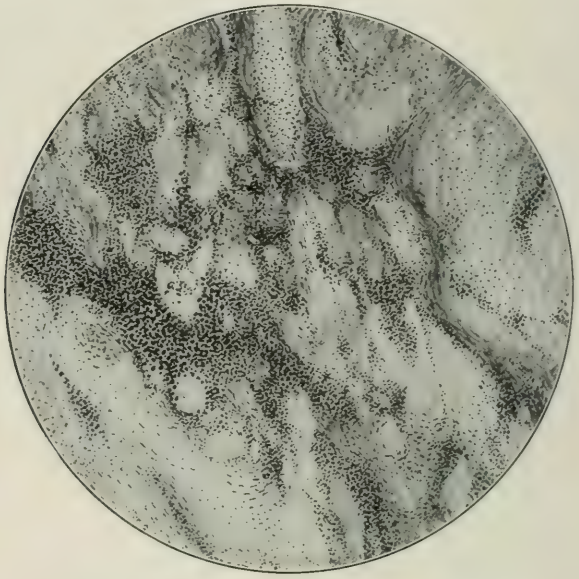

FIG. 3.—Section through the pyloric tumor. The connective tissue of the pyloric muscle is infiltrated with small polyhedral cells forming an anastomosing network and dividing the muscle bundles into large groups. (Small magnification.)

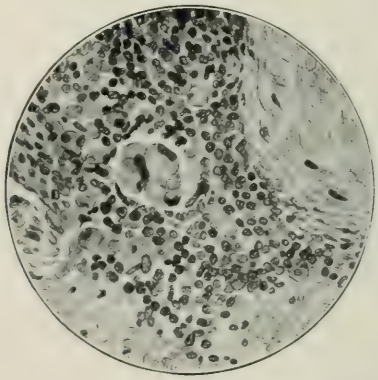

FIG. 4.—Same as Fig. 3. In the center a group of four cells are noticeable in which large mucous globules occupy the whole cell, pushing the nucleus to one side in crescent form. (Large magnification.)

nuclei and opaque acidophile cytoplasm. Many of them show large mucous globules which may occupy the whole cell, pushing the nucleus to one side

in crescent form. In several foci, especially in the fat tissue, there is definite formation of small alveoli lined by cuboidal epithelium. These appearances are characteristic of this type of gastric carcinoma. In wider extent they appear in the lesions known as linitis plastica."

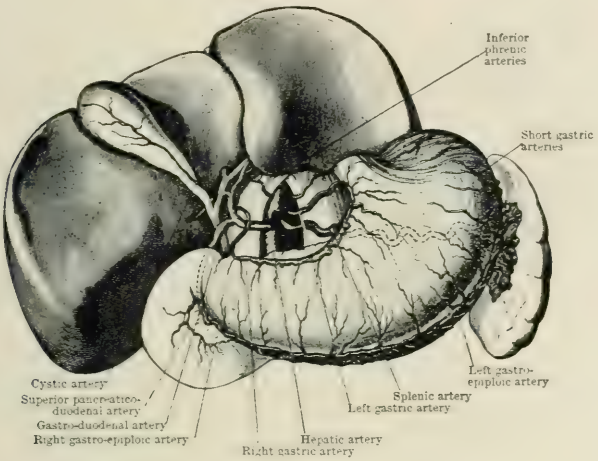

Fig. 5.—The celiac artery and its branches.

I am indebted to both Dr. Humphreys and Dr. Ewing for their kind reports.

To illustrate the state of the gastric mucosa, which was extremely congested and inflamed throughout and eroded all over, and the thickened pylorus, we give the following four drawings:

Epicrisis.—In considering the clinical picture of the disease, which consisted of a severe gastritis with pyloric obstruction and the last stages of cirrhosis of the liver, the following features are somewhat out of the ordinary and demand our attention:

1. The vomiting greatly exceeded the quantity ingested and persisted even when nothing was taken by the stomach. It contained neither HCl nor bile.

2. In this extremely emaciated man, who had lost over 70 or 80 pounds, the blood picture a few days before death shows 80 per cent. hemoglobin and over 5,000,000 blood corpuscles.

3. Notwithstanding the high degree of liver cirrhosis, there was no trace of ascites found in the abdominal cavity.

Vomiting in excess of fluids ingested is encountered off and on.

It is either due to hypersecretion of gastric juice or to a regurgitation of bile and intestinal juices into the stomach. In the case before us, however, neither of the two factors played a part. There was no ordinary gastric secretion present, as evidenced by the absence of HCl and the ferments, nor bile nor intestinal juice, as shown by the lack of biliary pigment or pancreatic ferment. Besides, the pylorus was stenosed to such a degree that nothing could enter or leave the stomach through this outlet. The vomitus was a watery fluid mixed with mucus, frequently tinged with blood, of slightly alkaline reaction. The characters of ordinary gastric secretion being absent in this fluid, it appears to me that we may explain the latter (gastrohydrorrhea) as an exudate due to the extreme congestion and accumulation of blood in the circulatory apparatus of the stomach.

For the development of hyperemia and extreme venous congestion in the latter organ, the conditions here were particularly favorable. If we take into consideration the intimate relationship between stomach and liver with regard to their blood supply, abnormalities in the liver will easily affect the stomach. This the more so as they both derive their inflow of blood from one and the same trunk artery, the "celiac."

In cirrhosis of the liver the connective tissue constricts the acini and also the arterioles with the result that the blood does not find an easy access here. It is dammed back and in consequence the blood from the celiac artery, instead of flowing into the hepatic artery which is already overfilled, enters in more abundant quantity the vessels supplying the stomach. In a similar manner, in complete pyloric stenosis, when the small intestine is empty and cut short from its work, the blood supply there will naturally be at a low ebb, and in consequence there will be a more active circulation in the bloodvessels situated higher up, namely, in the celiac artery and more particularly the gastric arteries. The venous supply of the stomach, on account of the difficulty of reaching the liver through the clogged-up portal vein, will likewise be overfilled—in the case before us—almost to bursting.

The regulatory arrangement of the organism can bring temporary relief by emitting some of the congested fluid in the circulatory

apparatus of the stomach through the walls of the latter into its cavity. Or there will be an exudation of fluid into the stomach, very much on the same order as the ascitic fluid in the peritoneal cavity in ordinary cases of cirrhosis of the liver without pyloric obstruction.

The process described appears to have happened in the case before us. The fluid exuded in the stomach was no gastric secretion, but rather a transudate. Accumulating in this organ and not being able to pass the pylorus, the liquid was then vomited.

The origin of the fluid explains in a satisfactory manner the two other anomalies here, namely, the absence of ascites and the good condition of the blood. The ascites was missing, as the act of liberating congestion took place in the stomach. The blood showed an almost normal amount of red blood cells, as the superfluous fluid was constantly drained off through the gastric walls.

In the case before us, in which gastric secretion was entirely missing, the gastrohydrorrhea was easily recognized. There is no doubt, however, that in other cases of cirrhosis of the liver accompanied by pyloric obstruction a similar transudation into the stomach or a gastrohydrorrhea takes place. The fluid, however, being mixed with gastric juice will not be easily recognized in its true light.

The following case I have recently observed will illustrate this point, also the relationship of pyloric stenosis and cirrhosis of the liver to the place of transudation (stomach, or peritoneal cavity). The case is briefly as follows:

November 30, 1915. Thomas M., about fifty-three years old, was always well until about a year ago, when he commenced to complain of fulness in the abdomen and slight nausea. Patient used to partake liberally of alcoholic beverages and smoked considerably. For the last five months there was vomiting, at first occasionally, and during the last two months almost constantly. The vomited matter in twenty-four hours frequently exceeded in quantity the total amount of ingested substances in the same period of time.

The examination showed an extremely dilated stomach (extending to the *symphysis*) with active peristalsis visible. There was constant ischochymia: HCl +, acidity = 40, much mucus. The liver dulness ceased three-fourths of an inch above the right costal margin. Patient com-

plained of great weakness, thirst, and vomiting. The duodenal bucket failed to pass the pylorus. The diagnosis of cirrhosis of the liver and obstruction of the pylorus—probably of a benign type—was made.

Patient was put on rectoclysis and no fluids given by mouth. Although the stomach was washed out daily, vomiting of a watery fluid, containing HCl and showing an acidity of about 30, was a constant feature. The whole quantity of ejected fluid would amount to one and one-half to two quarts daily. Apparently nothing could pass the pylorus. Patient had meanwhile lost over 80 pounds in weight. A surgical operation, although considered of great risk, had to be undertaken and was performed in my presence by Dr. Willy Meyer on December 8, 1915.

The pylorus was found completely stenosed, presenting an even swelling of thumb-size for one to one and a half inches; no swollen glands were found. A gastro-enterostomy was then established. After the operation patient did badly for about four days, continuing to vomit. Lavage was again instituted with great benefit. Nourishment was then given in small quantities and retained. December 16, diarrhea set in; patient, however, felt better and picked up in strength and general well-being. On December 24 ascites was observed in the abdominal cavity. Patient continued to gain in strength and weight, although the fluid in the abdomen likewise slowly progressed. Calomel and diuretin were given in order to hold the ascites in check. It never entirely disappeared, although there was considerable improvement in the condition of the patient.

The noticeable features in this case are: before the operation when vomiting was incessant there was no ascites. After the operation, as soon as the gastro-enterostomy opening put the intestinal tract into activity, ascites appeared, and there was no more vomiting.

The explanation here again is satisfactory if we assume that during the period of pyloric obstruction the vomited fluid relieved the congestion and was to a great extent in the nature of a transudate. As soon as the gastro-enterostomy established the activity in the intestines, the venous congestion was overcome by exudation of the dammed-back fluid through the intestine and omentum into the peritoneal cavity.

The frequent occurrence of vomiting in chronic alcoholic gastritis with cirrhosis of the liver (vomitus matutinus) may be due in part to a similar regulatory mechanism. The vomited matter would then represent to a certain extent transuded fluid and indicate a beginning faulty portal circulation.

DISCUSSION

Dr. Henry Sewall, Denver, asked if the gastrohydrorrheic fluid contained albumin.

Dr. H. A. Christian, Boston, said he had observed a similar condition in patients with ascites both with and without cirrhosis. He had always believed it to be a compensatory process for the elimination of fluid.

Dr. Max Einhorn, New York, said he had no doubt that the copious morning vomiting seen in many cases of cirrhosis and of cancer of the liver is due to failure of the portal circulation.

THE TREATMENT OF MIGRAINE

By B. K. RACHFORD, M.D.
CINCINNATI

It is my purpose in this paper to outline a treatment culled from my own experience as well as from the experience of others, which, I believe, if faithfully carried out, will result in the cure of the great majority of the cases of migraine and allied symptom groups.[1]

In beginning the treatment of migraine and allied disorders it is important to search for the chronic reflex and toxic factors that may play a role in producing these symptom groups. Such factors are often found in ocular defects, producing eye-strain; in abnormal conditions in the nose and pharynx, such as enlarged and diseased tonsils and adenoids; and in diseases of the teeth, the prostate gland, and the pelvic organs. In recent years I have been much impressed by the necessity of removing enlarged and diseased tonsils and adenoids. This is especially necessary in the treatment of migraine and recurrent asthmatic bronchitis, which latter occurs so commonly in children. In these cases the dietetic and other treatment may fall just short of a complete cure unless the diseased tissue of the adenoid ring is thoroughly removed. It is especially important in the treatment of severe migraine that all pathological conditions which may be a source of chronic toxemia should be carefully sought for and, if possible, removed. In recent years our attention has been especially called to the teeth, accessory sinuses of the nose, and the pelvic organs, including the prostate, as possible sources of such toxemias.

[1] In 1914 the writer read a paper on Recurrent Sibilant Bronchitis before the American Pediatric Society, demonstrating by a series of cases how readily this disease yielded to dietetic, hygienic, and medical treatment.

Dietetic Treatment. The most important bit of dietetic advice that can be given to a migrainous patient is that he should not eat too much; many of these patients are in the habit of eating much more than their caloric needs require, and as a result unnecessary work is demanded of the digestive and excretory organs. It is also most important that the character of the food taken should be easily within the digestive capacity. In short, the peculiarities of the digestive capacity of the gastro-intestinal canal of the patient should be carefully considered both as to quantity and character of food taken.

In addition to this bit of general advice, the idiosyncrasies of the patient should be studied with reference to his reaction (both digestive and metabolic) to various foods. No general rules concerning the elimination of certain foods can be laid down to enable the physician to determine the idiosyncrasies of the patient; for this reason in beginning the treatment certain foods may be eliminated which subsequent dietetic treatment may show had nothing to do with the production of the migrainous attacks.

In beginning dietetic treatment, therefore, it is wise to exclude all foods which experience has shown may be factors in the production of migraine, and later on when this symptom group has been controlled by treatment, certain of these foods may be gradually returned to the diet list. With these ends in view the following foods should be eliminated:

Eggs in every form, even in cooked foods, should be absolutely forbidden. Experience has amply demonstrated the fact that certain cases of migraine may be cured by this one rule of diet.

In 1910 Dr. S. J. Meltzer presented to the Association of American Physicians a paper on "Bronchial Asthma as a Phenomenon of Anaphylaxis," in which he advanced the theory that asthma was an anaphylactic phenomenon. In this paper Doctor Meltzer discussed the literature of anaphylaxis in its bearing on the theory.

It is also definitely known that the idiosyncrasy, which makes it possible for eggs to produce migraine, may be either hereditary or acquired, and it has also been definitely shown that this egg idiosyncrasy, after a period of abstinence sufficient to allow the individual to recover the normal physiological tone of his body

functions, may disappear to such an extent that the patient may acquire the power to digest and metabolize eggs without producing any of the symptoms of egg poisoning from which he formerly suffered, provided that he takes eggs in gradually increasing quantities, beginning with a very small amount.

In 1912 Dr. Oscar M. Schloss, in the *American Journal of Diseases of Children*, studied the subject of egg poisoning as an anaphylactic phenomenon, and called attention to the fact that the patient might be immunized against this poisoning by giving him minute but gradually increasing doses of ovomucoid.

Sweets should, for a time at least, be almost if not quite eliminated from the diet. It is established beyond question that the stopping of an excessive intake of sweets results in the immediate improvement of many patients suffering from migraine.

Shell-fish of all kinds are to be excluded. The literature of medicine is full of examples of migraine, asthma, and urticaria being produced by shell-fish. In 1899 Dr. Frederick A. Packard, under the title of "Urticaria of Mucous Membranes," presented to the American Pediatric Society the then existing clinical evidence of the mutual relations of asthma and urticaria.

Butter fats (cream and butter) should also be eliminated from the diet, and in certain cases it may be necessary for a time to exclude milk absolutely.

Raw fruits and raw vegetables are to be avoided, especially strawberries, oranges, rhubarb, and tomatoes, since medical experience teaches that attacks of migraine and allied disorders are not infrequently precipitated by the taking of these foods.

In addition to the foregoing special articles of diet, it is wise also to avoid rich and highly seasoned foods of all kinds, and tea, coffee, and alcohol, if taken at all, should be used in moderation.

The following foods may be allowed: Beef, mutton, fowl, cereals, bread, all cooked vegetables, not already proscribed, cooked fruits, skimmed milk, and thick soups.

This dietetic treatment is to be followed for some weeks or months until the patient has apparently recovered. Then follows a relaxation of the dietetic treatment along lines suggested by conditions presented by the patient, until perhaps at the end of three or four

months most of the proscribed foods, excepting eggs, may be given in moderate quantities. Following this, if the patient remains well, eggs may be carefully added to the diet in small quantities.

Hygienic Treatment. The patient should live out of doors as much as possible, that is to say, he should have the best air available, night and day, consistent with his occupation. Patients who live in school rooms, factories, and shops during a large portion of the day should have all of the air possible at night. Exercise in the open air is necessary. In prescribing exercise, the needs of the patient should be considered.

Medical Treatment. In beginning the treatment it is advisable that the patient's bowels should be kept open with some saline laxative; for this purpose sodium sulphate or phosphate or some preparation of magnesium should be used. When the constipation is severe, magnesium sulphate is advisable. This may be given in one of the mineral waters or in any combination which the physician may devise. In children, milk of magnesia may be used with advantage. In adults and older children I still prefer and continue to use a formula which I originated many years ago for the treatment of migraine.[1] It is as follows:

℞—Sodii sulphatis (dry)	gr. xxx
Sodii salicylatis (from wintergreen)	gr. x
Magnesii sulphatis	gr. l
Lithii benzoatis	gr. v
Tincturæ nucis vomicæ	♏iij
Aquæ distil. q. s. ad	℥iv

M. Ft. mist. sig. Take, half an hour before breakfast, a sufficient quantity to produce at least one bowel movement during the morning.

The prescription is put up in siphons and charged with carbonic acid; long experience has taught me that it is of great value in the prevention of migraine and allied disorders. After a few weeks or months the saline laxatives may be replaced by cascara, phenolphthalein, or some other palatable laxative, that is, if the constipation continues. In many of these cases I have used the mineral oils with success after the treatment is well under way.

It is of prime importance in all cases to give alkalies. The simplest

[1] Medical News, October 3, 1903, Rachford, Diseases of Children, 1912.

and best preparation of this kind is perhaps sodium bicarbonate. This may be prescribed in capsules in 5- or 10-grain doses, three times a day, according to the age of the patient, taken with a large goblet of water. The soda should be taken preferably an hour before meals or at bedtime. If the patient prefers, the alkalies may be given in the form of one of the alkaline waters, such as Vichy. It should be remembered that the alkali is an important part of the treatment, not only in the beginning, but for months and even years. The patient should also cultivate the habit of drinking water frequently throughout the twenty-four hours.

THE VITAL CAPACITY OF THE LUNGS, AND ITS RELATION TO DYSPNEA IN HEART DISEASE

By FRANCIS W. PEABODY, M.D.

AND

JOHN A. WENTWORTH, M.D.

BOSTON

Recent investigations on the cause of dyspnea[1] in heart disease have been directed, in the main, toward the chemical aspect of the regulation of respiration. It has been shown that a change in the chemical composition of the blood may be an important factor in the production of dyspnea in certain cases, but the results indicate that this is not alone sufficient to explain the clinical condition. Another significant feature in the production of dyspnea relates to the mechanical changes in the respiratory movements.

The importance of the mechanical factor was brought out by a series of observations made by one[2] of us on normal subjects and of patients with cardiac disease, in whom dyspnea was produced by increasing the concentration of carbon dioxide in the inspired air. It was found that the patients with heart disease became dyspneic when breathing much lower concentrations of carbon dioxide than was the case with normal subjects, and an analysis of graphic records of the respiration showed that the essential difference

[1] The term dyspnea as used applies not to rapid respiration or to deep respiration but to the subjective sensations of discomfort which result when both an increase in rate and in depth have raised the amount of air breathed—the so-called minute volume of air—to what approaches the maximum of which the patient is capable.

[2] F. W. Peabody, "Clinical Studies on the Respiration, No. 1. The Effect of Carbon Dioxide in the Inspired Air on Patients with Cardiac Disease." Arch. Int. Med., 1915, xvi, 846.

between the two groups consisted in the fact that normals could increase the minute-volume of air breathed much higher than could the pathological subjects. Thus the normals became dyspneic when they were breathing 70 to 80 liters of air per minute, while the cardiac patients became dyspneic when they were breathing only 40 or even 20 liters per minute. The degree to which the minute-volume of air breathed can be increased depends, of course, on the ability to increase the rate and volume of respiration, and it was found that the chief handicap of the cardiac patients consisted in the fact that they were unable to increase the depth of respiration as well as the normals. This inability to breathe deeply corresponded to a decrease in the vital capacity of the lungs.

Similar results have been obtained with subjects performing moderate amounts of standardized exercise. In the test which has been applied, and which consists in walking a short distance at a definite rate, the minute-volume of normal persons increases to nearly three times their minute-volume while at rest. By increasing the rate and depth of respiration slightly, they are able to accomplish this without any feeling of dyspnea. In cardiac patients there is a very similar relationship between the volume of air breathed at rest and while taking the test exercise, but even the slight increase in the rate and depth of respiration brought about by the rise of metabolism is sufficient to cause the subjective feelings of dyspnea. The actual volume of the individual respiration does not increase greatly, but it approaches more closely to the maximum of which they are capable, on account of the abnormally low vital capacity of the lungs.

It has long been known that the vital capacity of the lungs is decreased in many persons with cardiac disease, but the bearing of this fact on the production of dyspnea has been, to a great extent, lost sight of. A somewhat extensive study of the subject has therefore been undertaken, and an attempt has been made to correlate the decrease of vital capacity with the clinical condition of the patient, especially with regard to the production of dyspnea.

All observations were made with a calibrated spirometer, the movements of which are recorded on the smoked drum of a kymo-

graph. Normal standards have been established from observations on 103 healthy young men and women. There is a great variation in the vital capacity of normal persons, but after grouping the results according to sex, and according to height, it was found that 93 per cent. of the normals had a vital capacity which was 90 per cent. or more of the standard normal of their group. Certain individuals, notably those who had undergone much athletic training, had a vital capacity considerably above the normal figure, but from the present point of view this is unimportant, as in the pathological cases it is the decrease in vital capacity which is significant.

Group.	I.		II.		III.		IV.	
Vital capacity, per cent.	90+		70–90		40–70		40–	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
No symptoms . . .	17	95						
Working	..	..	20	87	7	18		
Not working . . .	1	5	3	13	32	82		
Decompensated . .	..	..	..	..	..	..	18	100

It has been possible to study and classify, up to the present, 169 observations on the vital capacity in 95 subjects with heart disease. The observations have been divided into four groups, according to the percentage of the vital capacity in terms of the normal standard for the sex and height of the patient. (See Table.) Thus in Group I the vital capacity is 90 per cent. or more of the normal; in Group II it is 70 to 90 per cent.; in Group III it is 40 to 70 per cent.; and in Group IV it is below 40 per cent. of the normal. A close correspondence exists between the vital capacity and the clinical condition. Patients entering the hospital with acute cardiac decompensation have a very low vital capacity. Clinical improvement is associated with a rise of the vital capacity. With failure to improve the vital capacity remains stationary. The development of more serious symptoms in a compensated patient is usually associated with a fall in the vital capacity. The Table shows briefly the relation of the vital capacity to the clinical condition in 87

patients who could be classified on the basis of their symptoms. Eleven patients are classified in more than one group, depending on their clinical condition at the time when the observations on the vital capacity were made. Of the patients in Group I with a vital capacity of at least 90 per cent. of the normal, 95 per cent. showed no abnormal tendency to dyspnea. One man was unable to do much, but dyspnea was not the essential feature in his case. Of the patients in Group IV, with a vital capacity of less than 40 per cent., all were decompensated and became dyspneic on very slight exertion. All were bed patients. The patients in Group III were severely handicapped by dyspnea. Almost all could get about a little, but 82 per cent. were unable to do any work, and of the 18 per cent. who were working, the majority could do very little. Of the patients in Group II, on the other hand, 87 per cent. were able to work, the majority leading a more or less normal life, limited only by the fact that dyspnea is almost always produced in them much more easily than in normal persons. Only 13 per cent. were unable to work.

It is thus evident that in most patients with heart disease there is a very intimate relation between the vital capacity and the limitation of functional efficiency. Decrease in the vital capacity is an important factor in explaining the production of dyspnea in cardiac patients. The determination of the vital capacity has a practical value in that it gives a quantitative index which is a fairly good guide as to the amount of exertion which a patient can undertake without becoming short of breath. Often it is much more significant than is the history obtained from the patient. The variations in an individual case correspond to changes in the clinical condition, and are of interest in prognosis and treatment. While the vital capacity does not, of course, serve as a complete index of the functional capacity of the heart, since there are many features of cardiac pathology to which it bears no relation, it nevertheless gives important information as to certain aspects of the circulation. The cause of the variations in the vital capacity is not, at present, wholly clear, but they probably relate to conditions in the pulmonary circulation. (Siebeck.)

DISCUSSION

Dr. Henry Sewall, Denver, asked if the speaker had found that training produces any marked effect upon vital capacity.

Dr. Francis W. Peabody, Boston, said that the effect of training on vital capacity is very marked indeed. It often raises the vital capacity much above the normal figures. This does not affect the clinical significance of the vital capacity in heart disease, however, as in this condition the figures tend to be below normal.

ACUTE EXPERIMENTAL POLYCYTHEMIA: FURTHER OBSERVATIONS ON THE PART PLAYED BY THE LIVER

By PAUL D. LAMSON, M.D.
BALTIMORE

(Abstract)

In an article previously published by the present author it was shown that in acute experimental polycythemia produced by the intravenous injection of epinephrin the increase in number of erythrocytes per unit volume of blood there observed is brought about by some action of the liver. It was pointed out that this polycythemia is due in part to a decrease in plasma volume, and a consequent relative increase in number of red cells per unit volume of blood, but as this decrease in volume is not of sufficient magnitude to entirely account for the increase observed in number of erythrocytes, and as no evidence of the new formation of red cells was observed, it was deduced by exclusion that a reservoir of erythrocytes must be present in the body, and the location of this reservoir was experimentally shown to be in the liver. In the paper very briefly presented before this Society, additional proof was given of the localization of this process in the liver, the presence of a reservoir of erythrocytes in this organ, and the interesting fact that the plasma volume and blood volume may vary independently of the number of erythrocytes per unit volume of blood. As these results have since been published in detail, the reader is referred to these articles for a complete account of the experimental results.

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DISCUSSION

Dr. Henry Sewell, Denver, suggested that the presence or absence of normoblasts might be of significance in the artificial polycythemia induced by Dr. Lamson.

Dr. Paul D. Lamson, New York, said that normoblasts were not found.

ACTION OF OPIUM ALKALOIDS INDIVIDUALLY AND IN COMBINATION ON THE VOMITING CENTER[1]

By DAVID I. MACHT, M.D.
BALTIMORE

(By Invitation)

Nausea and vomiting are among the commonest sequelæ which the physician encounters after administration of morphin. These untoward symptoms, occurring even after small doses of morphin, although not dangerous in themselves, are disagreeable enough to be largely responsible for the employment of other opiates in its stead, either in the form of individual alkaloids such as codein, or dionin, or of their combinations such as the commercial preparations called narcophin and pantopon.

In connection with pharmacological studies of the action of the principal primary opium alkaloids individually and in combination with each other on the circulation,[2] respiration,[3] and pain[4] which have already been published, the author has undertaken to investigate the comparative roles played by them in the production of vomiting. To that end a large number of experiments on animals were performed and later a series of clinical observations were made.

[1] From the Pharmacological Laboratory, Johns Hopkins University and the James Buchanan Brady Urological Institute, Baltimore.
[2] Macht, Jour. Am. Med. Assn., 1915, lxiv, 1489.
[3] Macht, Jour. of Pharmacol. and Exp. Therap., 1915, vii, 339.
[4] Macht, Hemon, and Levy, ibid., 1916, viii, 1.

For experimental purposes in this connection the most suitable animal for study is the dog, as it is well known to pharmacologists, that the vomiting center in this animal responds to the effects of morphin almost as promptly as to the effects of apomorphin, our most important centrally acting emetic drug.

On injecting dogs with the seven principal primary opium alkaloids—namely, morphin, codein, narcotin, papaverin, narcein, thebain, and cryptopin, it was soon found that in respect to their emetic action, they fall into two groups: on the one hand, morphin which produces vomiting very easily and in small doses, and on the other hand, all the other alkaloids which induce vomiting very rarely, even after large doses. Thus, doses of 50 to 100 mg. of codein per kilo were not followed by emesis, whereas doses of morphin 0.4 mg. per kilo usually produced vomiting.

It was next undertaken to determine the minimal dose of morphin per kilo required to produce vomiting. Here considerable individual variations were found in different dogs. The minimal dose of morphin to prove effectual in a few cases was 0.15 mg. per kilo. Some animals, on the other hand, required as much as 2 mg. per kilo, but the usual emetic dose of morphin was found to be between 0.3 and 0.4 mg. per kilo weight of dog. In order to approximate conditions as nearly as possible those in the clinic all the injections were given either subcutaneously or intramuscularly. The above doses of morphin not only induced vomiting, but were found subsequent to the emesis to paralyze or put out of commission the vomiting apparatus so that, except after subminimal doses of morphin, a subsequent injection of apomorphin was not effectual.

Parallel with the morphin experiments, a series of observations on the same animals on different days were made with injections of combinations of morphin and narcotin in different proportions and with the commercial preparation of morphin and narcotin marketed under the name of narcophin. Here again all injections were made in the muscles or under the skin. A remarkable phenomenon was noted. It was found that a combination of morphin and narcotin did not produce vomiting as often as the same dose of morphin did when administered alone, and that even larger doses

of morphin could be injected combined with narcotin without the production of emesis. Furthermore, it was noted that such a combination tended less to put the vomiting mechanism out of commission than morphin alone, so that a subsequent injection of apomorphin was usually effectual and produced vomiting. The average dose of morphin that could be administered in combination with narcotin without producing vomiting was 0.5 mg., but doses as high as 2 mg. and more were sometimes given with the same result.

A similar action was noted after combinations of morphin and papaverin.

Even more striking was found to be the behavior of morphin administered in the form of total opium alkaloids. In this combination doses of morphin much larger than the usual emetic doses of that alkaloid could be administered without the production of vomiting and without paralyzing the vomiting center, as indicated by its response to a subsequent injection of apomorphin. The explanation of this phenomenon is probably the same as in the case of respiration, described elsewhere.[1]

Following the experiments on lower animals, a series of observations were made on the author himself and some co-workers, and later, on ambulant patients in the Brady Urological Institute, to whom small doses of morphin, narcophin, or total opium alkaloids were administered by injection, with their consent, as a sedative preparatory to various minor surgical manipulations, such as circumcision, cystoscopy, incision of buboes, passing of sounds, etc. Here it was found that morphin given alone produced nausea much oftener than when given in combination with narcotin or in the form of total opium alkaloids. Five milligrams ($\frac{1}{12}$ gr.) of morphin were in some cases sufficient to produce nausea. On the other hand 20 mg. of Sahli's combination (=10 mg. of morphin) seldom produced any nausea or vomiting.

An exhaustive examination of the literature on the subject was found to confirm the author's experiences.

The full account of this investigation will appear in the *Journal of Pharmacology and Experimental Therapeutics.*

[1] Macht, Jour. of Pharmacol. and Exp. Therap., 1915, vii. 399.

DISCUSSION

Dr. R. H. Babcock, Chicago, said that he had used pantopon by hypodermic with most gratifying results; it has a better somnifacient effect than morphine and it acts better upon cardiac patients than does morphine.

Dr. David I. Macht, Baltimore, said that pantopon has been found to serve as an excellent anesthetic for experimental dogs.

OBSERVATIONS ON THE STARVATION TREATMENT OF DIABETES

By C. F. MARTIN, M.D.
AND
E. H. MASON, M.D.
MONTREAL

For the past year we have been treating all cases of diabetes admitted to the Royal Victoria Hospital on the starvation plan.

Those patients who remained under the strict supervision, and those who, when away, made an intelligent effort to carry out the treatment, did well, and have remained sugar-free on the prescribed diet, proved after varying periods to be suited to their tolerance.

Difficulties, however, arose with those unwilling, or unable, to follow the directions, and these difficulties, needless to say, were numerous. No doubt the supreme difficulty will always be that either the patient or the doctor fails to appreciate the need of strict attention to the treatment. So much precision in the diet is necessary, for severe cases, that even in the hospital routine it has often been extremely difficult to carry out a successful treatment except with full coöperation of the patient.

Again, our knowledge of the exact values of foodstuffs is still insufficient, more especially that branch relating to appreciation of the values of cooked and uncooked foods, notably the carbohydrates, and the proteins with their CHO content.

That there is greater need of standardization in our dietetic treatment is more and more apparent, and without an attempt to make clear the values of foods given, it is difficult for observers to fully coöperate in work of this nature.

The simple example may be cited of CHO values in various vegetables; while some observers compute in their estimate of CHO

food administered only the available CHO, others again include the total amount, of which unused cellulose forms a considerable portion and alters entirely the value of our given foods. So, too, with boiled vegetables, while some compute the water in which CHO are boiled, others discard it, even though a not inconsiderable amount of available food in it should be estimated if we are to aim at exactness in our computations.

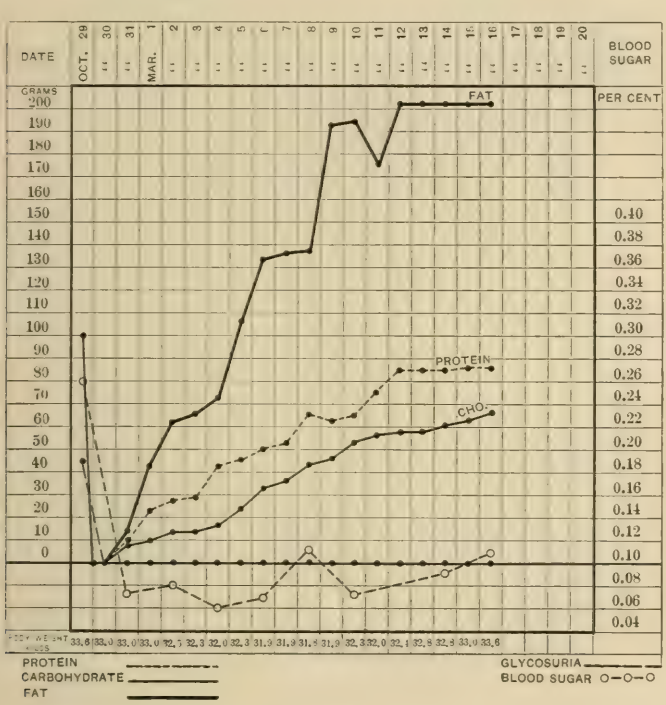

CHART I

On the other hand, it is a matter of occasional surprise that patients can sometimes disregard these dietetic prescriptions with impunity. Particularly noteworthy is an instance of a patient with moderately severe diabetes, upon whom, after successful starvation treatment had conferred benefit, periodical alcoholic bouts and late nights of dissipation seemed to have no deleterious effects.

In two of our cases, however, fatigue and nervousness seemed to markedly aggravate an already existing hyperglycemia, this view coinciding with those recently emphasized by Cannon (see Chart I).

In one much-worried patient, with a glycosuria of 12 per cent., rest and relief from anxiety alone were followed by a reduction to 2 per cent. on the following day.

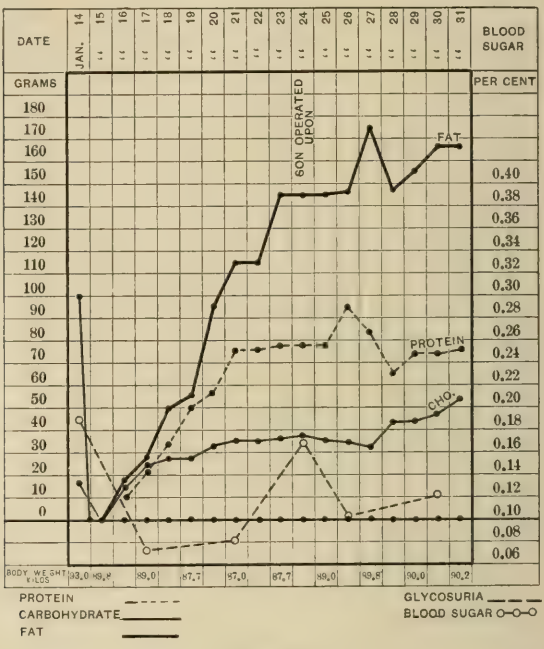

CHART II

As a rule one or two days of starvation sufficed to render the urine sugar-free, and in only one instance was the period as long as five days.

In the moderately severe cases it was found that patients could be raised to a tolerance of high caloric value in an amazingly short time (see Chart II), but it has not seemed possible in raising the CHO tolerance to avoid the return of a hyperglycemia. In fact, in our limited experience it would seem that the metabolic disturbance which is implied by the term diabetes is not eradicated by any

dietetic treatment, but merely subdued during the period of absolute precise treatment.

During the starvation treatment it was not found necessary, except in one instance, to use alcohol during the early days of treatment. In one case (Chart II) all forms of foodstuffs were raised to a very high level of value, and maintained with excellent results, while the patient was under supervision; but, as a rule, it was found that the more gradual and slow-attaining of tolerance seemed the wiser plan, and when accompanied by a weekly starvation day, the level of tolerance was raised with much greater success.

In the satisfactory cases the striking features were the speed at which sufficient satisfying food could be given, and the patient maintained upon a low level of food supply with an absence of hunger, thirst, fatigue, or loss of weight, and a general feeling of well-being seemed to exist when the proper level was maintained.

During the early treatment the loss of weight seemed rarely to be marked—in one case over 20 pounds, and in two others 13 pounds—while in the rest the loss of weight never exceeded 5 pounds. Later on the normal weight was either recovered or remained but little below the original level. Perhaps insufficient attention has been drawn to this fact, and the impression is too wide-spread that the starvation treatment is one of reduction with severe emaciation, whereas in reality the subjective and objective evidences of starvation are not present.

Examination of Blood-sugar. The *blood-sugar* was periodically examined in every case. After the patient's admission an estimate was first formed of the approximate severity of the disease, together with the percentage of blood-sugar, and then 100 grams of glucose were given on the first day of starvation, and the blood-sugar thereafter determined every hour for four hours. Experience in the case of three or four patients, however, revealed the fact that four hours was an insufficient period in which properly to estimate the blood-sugar curves. We have recently extended these observations to cover twelve to twenty-four hours, and discovered thereupon that the hyperglycemia is more persistent than had been supposed.

The results by comparison with normal individuals were of great interest.

Experimental Glucose Curve of Normal Individuals. In the *normal* person there is, of course, an increase of blood-sugar after 100 grams of glucose have been administered, but the curve occupies a much lower level, usually dropping *below* the normal in two or three hours. The maximum is attained at the end of the first hour, becomes normal again at the second hour, goes below the normal at the end of the third hour, and finally rises again to normal in four or five hours (see Chart III).

The *normal threshold* we regard as 0.14 per cent.

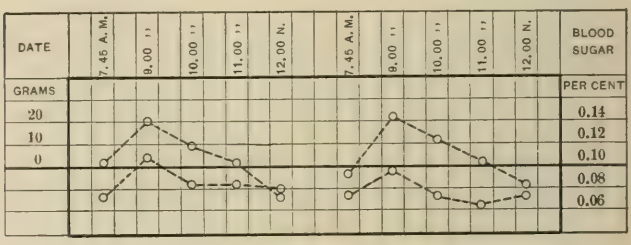

Chart III

Experimental Glucose Curve of Diabetics. In diabetes, however, the curve was markedly altered and prolonged, as was found in repeated observations, in which, of course, we kept all individuals under exactly uniform conditions.

One hour after administration of the glucose the percentage rose, attaining its maximum at the end of the second hour, rarely at the end of the third.

The decline followed, but at a rate much slower than in normal individuals. The implication is that in diabetes, the liver not being able to hold the sugar in amount and duration as in the normal, causes a higher percentage of blood-sugar to appear.

The excursion is greater, the ascent more acute, the maximum appearing sometimes rapidly, sometimes more slowly, the variations, however, not depending on severity. As a rule the maximum was reached at the end of two hours, and the decline was slow, occupying often eight to twelve hours (see Chart IV).

These observations seem to confirm those of Falta, who emphasized their importance in diabetes.

The abnormally slow decline in the blood-sugar curve in the later hours of the test on diabetics possibly suggests some kind of *kidney block*, and varies according to the renal threshold and in part, too, of course, to the degree of combustion (see Charts IV and V).

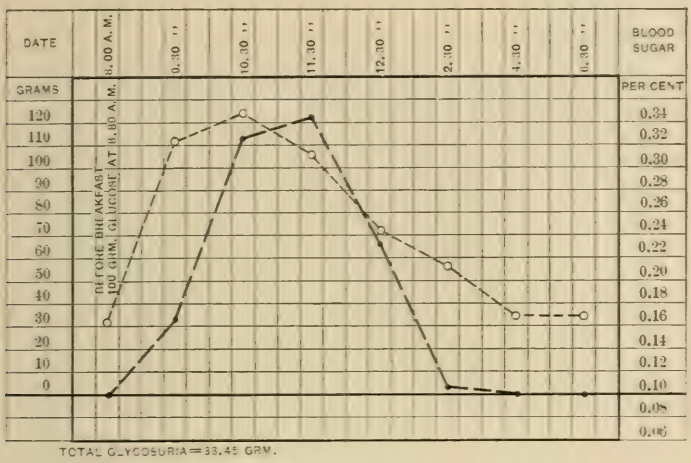

CHART IV

RENAL BLOCK. This question of kidney block is apparently an unsolved problem, but the more careful and repeated examinations for blood-sugar have demonstrated its importance, as well as the intimate relation in many cases between glycosuria and renal function. It was that with starvation the disappearance of the glycosuria has usually preceded the subsidence of hyperglycemia. However, our experience in one respect is at variance with Joslin, who states that during starvation the hyperglycemia persisted, while in the majority of our cases it disappeared rapidly with starvation.[1]

With gradual increase in the diet, however, the blood-sugar rose to an abnormal degree, usually in the absence of glycosuria.

Various factors seem to play a part in inducing block, and the

[1] Arch. of Int. Med., vol. xvi, 703.

causes are difficult to explain; in three of our cases the values ran as high as 0.22 per cent., 0.26 per cent. and 0.28 per cent. without glycosuria. In other cases with glycosuria of long duration the block appeared, though at a lower level.

A certain prognostic importance may be attached to renal block in diabetes, for it would seem that the degree of hyperglycemia varies directly with the tendency to progression, and the development of complications.

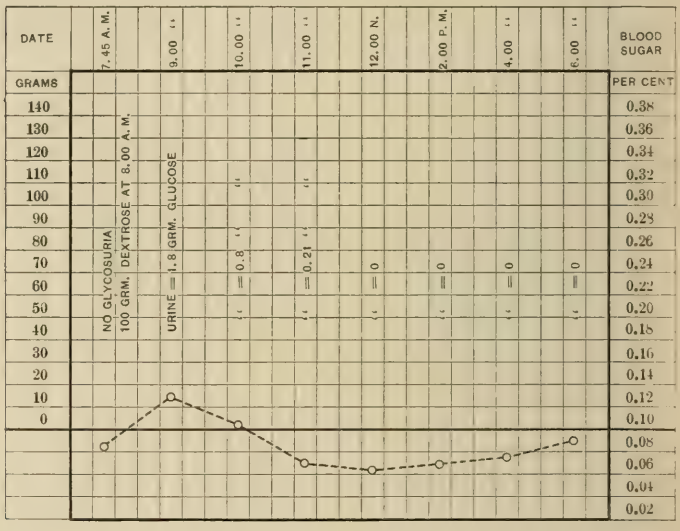

CHART V

An insidious and progressive diabetes may often be overlooked when glycosuria is absent, and where an appreciation of the block may yield a more intelligent means of dealing with the patient.

Evidently sufficient stress is not laid upon the hour at which these estimates are made. Thus, for example, the hyperglycemia came on at first about two hours after meals, at which time we think the estimates should always be made as giving us the best guide to the diabetic changes. Blood-sugars in the majority of our diabetics were found to be normal in the early morning before breakfast, while two hours after meals a hyperglycemia was evident, this

depending, of course, in part upon the diet. Often, however, where the diet was restricted in accordance with the treatment the same experience occurred.

The following figures will indicate the differences:

Before breakfast.	After breakfast.
.11 per cent.	.15 per cent.
.10 per cent.	.16 per cent.
.18 per cent.	.24 per cent.

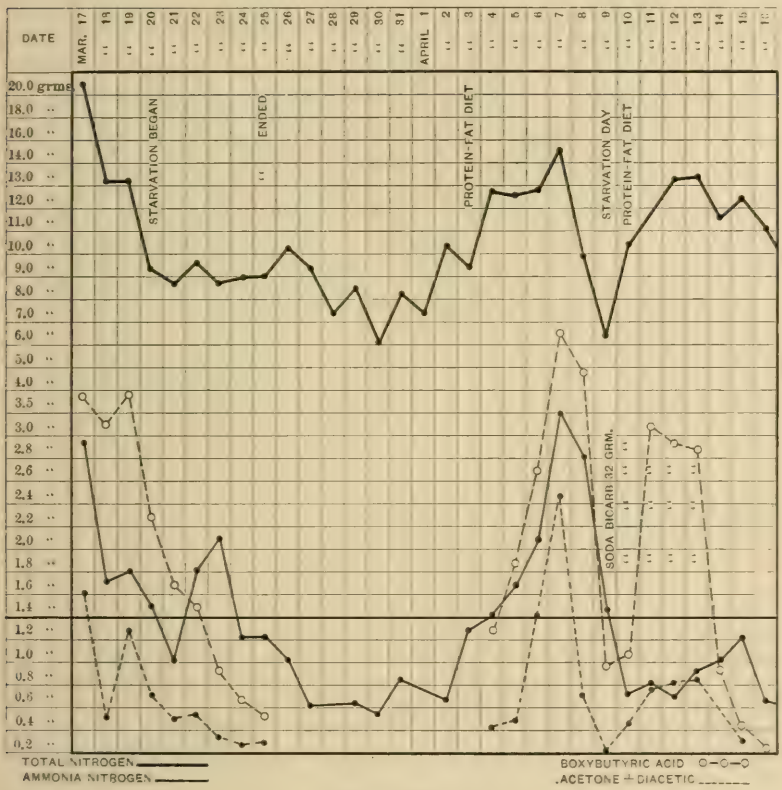

CHART VI

RENAL GLYCOSURIA AND BLOCK. In one of our patients, persistent glycosuria appeared whenever the blood-sugar rose to a level of 0.11 per cent.; at no time was there much glycosuria, and he always reacted to starvation; 27 grams of carbohydrate per day would

induce a glycosuria, which was not increased with an intake up to 50 grams.

Before meals his blood-sugar was 0.08 to 0.09 per cent., while after a mixed meal his blood-sugar rose to 0.11 or 0.12 per cent. with slight glycosuria (see Chart VI).

As a result of recent work, no doubt, the more frequent estimations of blood-sugar will demonstrate that renal diabetes, so-called, is less rare than has hitherto been believed.

Test Diet. In some cases a patient's tolerance seems to alter in a very short time, and appreciation of this is of the greatest importance in the use of test diets. Thus, for example, in one individual who had had a fat protein diet for three days, preceded by a low CHO intake for one week, there was a D : N ratio of 2.77, showing an inability to burn 43 per cent. of protein carbohydrates. He continued on a fat-protein diet for twenty-one days, and during the first fourteen days the D : N ration varied markedly, finally dropping to zero on the sixteenth day. On this day he burned 36 grams of protein CHO as well as 2 grams of CHO in 100 grams of chicken (*i. e.*, 38 grams CHO).

Reading the variations according to the Lusk-Falta formula we found the following:

$$\frac{35.9 \times 100}{12.97 \times 3.65 + 0} = 75.6$$

Thirteen days later:

$$\frac{3.08 \times 100}{9.32 \times 3.65 + 2} = 8.5$$

Acidosis. Two important points are worthy of note in our observations:

1. The ferric chloride reaction is sometimes absent when acidosis is present, and is less sensitive, too, than the nitroprusside reaction.

2. The urine does not always show a reaction for acidosis even when the blood gives a positive quantitative result. This latter is important as reminding us that the excretion of the acid bodies is not necessarily an index of the degree of acidosis.

Starvation in the ordinary individual usually results in acidosis, while in diabetes the reverse occurs. Allen, indeed, lays stress on

this feature, and insists on the need of eliminating ketone bodies from the blood by means of starvation.

Sometimes, however, in our cases, acidosis was initiated by the starvation, at other times a preëxisting acidosis was increased, though usually it disappeared. Evidently there is a variation due to many circumstances, though starvation ultimately does make the urine acid-free.

In one persistent case of very mild diabetes, with prolonged mild acidosis, interrupted periods of a fat-free diet seemed especially useful in clearing up remnants of the acidosis.

In one very severe case in which the acidosis disappeared on starvation, it developed again on a protein-fat diet, and later on disappeared with one day of starvation. Sodium bicarbonate was given (32 grams per diem) for five days, with resulting elimination of more ketone bodies. Excretion of these bodies ceased again with cessation of bicarbonate administration.

Another experience worthy of note is the varying ratio of the acetone bodies to β-oxybutyric acid. Sometimes there is much acetone and little β-oxybutyric acid, and sometimes the reverse occurs. There seems to be little constancy, and the percentage of 60 to 80, as usually recorded, is subject to many wide variations, depending upon the severity of the acidosis.

DISCUSSION

Dr. S. J. Meltzer, New York, said he thought there would be no discussion this evening or he would have discussed Dr. Hamman's as well as Dr. Martin's papers. His own studies with Dr. Kleiner led him to conclusions which greatly coincide with those of Dr. Hamman. He wished to answer frankly Dr. Jacobi's question: he knows at least of one patient who may have lived comfortably for some time with glucose in the urine; but who was starved, developed acidosis which was not discovered early, and died. I believe that Dr. Stillman published such a case. The statement is made that such fatal cases need not occur if the acidosis were discovered in time. I doubt whether this statement is valid. At any rate we ought at least to draw the conclusion that the starvation treatment

ought not to be used indiscriminately, and ought to be used only in a hospital where competent physicians would be constantly on the lookout for the first signs of acidosis. Furthermore, it does not seem to him that the words acidosis and dying ought to be used synonymously. Poulton described recently cases of diabetes, 2 of which showed considerable acidosis, and were nevertheless doing fairly well, while 2 other cases which died from diabetes did not show any sign of acidosis.

Dr. A. Jacobi, New York, said it seemed to him that the starvation treatment of diabetes is very satisfactory to the experimenting doctor; but what happens to the patient? He had seen patients with 5 or 6 per cent. of sugar go along in satisfactory health for five to ten or even twenty years. He had seen a few starved patients, rapidly emaciated, suffering from cerebral anemia, complaining bitterly of other symptoms of nerve exhaustion, and now they are dead. They wouldn't be dead if they had not been starved. Are not those patients with glucose in the urine better off than those that died? He would like to know whether more or less diabetic patients in the practice of others have died in the past few years.

Dr. D. D. Van Slyke, New York, said that the diabetic cases placed on the fasting treatment at the Rockefeller Institute are watched very carefully. Most do not develop acidosis while fasting, but some do. It can be detected by plasma bicarbonate determinations before it becomes dangerous. The fast is always broken off as soon as the approach of acidosis is observed. It is a peculiar fact that a patient may develop acidosis on his first fast, but endure the second and become sugar-free without a repetition of the acidosis.

Dr. M. Howard Fussell, Philadelphia, said he had used the starvation treatment in a number of cases during the past year; under conditions of which Dr. Jacobi inquires whether all of them were treated in hospitals; all have done extremely well. Some have had severe acidosis, but all came out satisfactorily and all are now as comfortable as possible.

Dr. C. F. Martin, Montreal, said that Dr. Joslin had answered Dr. Jacobi's question as to the present mortality rate of diabetes in the discussion of acidosis yesterday. He was sorry that Dr. Jacobi had got the idea that he actually starves his patients; as a matter of fact they are not even hungry, they are not fasted to that extent.

STUDIES OF THE STOMACH IN SYPHILIS

By FRANKLIN W. WHITE, M.D.
BOSTON

(Abstract)

The wide use of serum tests in the last five or six years has permitted us to discover a greatly increased number of persons with syphilis, some of whom have prominent symptoms referable to the stomach, or actual stomach lesions.

In such a group of cases we have studied the functions of the stomach, the coincidence of syphilis with other diseases of the stomach, its relation to peptic ulcer, and the symptomatology.

Material. In a group of 600 cases of syphilis with strongly positive Wassermann reaction (largely patients at the Boston City Hospital, with the addition of a small number of private patients) were found 44 with prominent stomach symptoms, after excluding patients with hepatic cirrhosis, gumma of liver, nephritis and tabes.

In 35 cases no definite lesion of the stomach was proved, in 9 actual syphilitic or coincident lesions were found (ulcer, gumma or cancer).

It is often impossible to distinguish between syphilitic and coincident stomach lesions during life. Two cases were proved cancer at autopsy, 5 had ulcer, syphilitic or coincident, 2 had syphilitic induration or gumma.

In the first group with no proved lesion of the stomach there were no characteristic symptoms. The most common were epigastric distress, burning or pain, occasionally relieved by food or alkalies, vomiting, anorexia, loss of weight, usually moderate. The symptoms were as often intermittent as persistent, and the course

not steadily progressive. No attempt was made to classify the cases by variations in the history.

The gastric secretion after the Ewald breakfast was within normal limits; in 23 cases (65 per cent.); hyperacid in 5 cases (15 per cent.); and subacid in 5 cases (15 per cent.); while 2 cases (5 per cent.) showed no free HCl. Only 1 case showed twelve-hour food residue. There was no blood in stomach contents or feces with the benzidin test. These changes in gastric secretion are not distinctive and are much like those in any functional or toxic group of cases of the same age and sex in which digestive symptoms are common; for example, neurasthenia, or tuberculosis.

There may have been a chronic gastric catarrh in some of the cases, but with no positive signs. Since the free use of the Wassermann test many cases with digestive symptoms and positive serum are classed as syphilis of the stomach, probably without reason.

In the group of 9 cases with syphilis and proved stomach lesions, the classification has been very difficult. Two cases were proved at autopsy to be cancer of the stomach, but during life it was absolutely impossible to make a positive diagnosis between syphilis and cancer by history, physical examination, lack of gastric secretion, *x*-ray defect or even the appearance of the stomach at operation. One was a plum-sized medullary cancer, the other a scirrhous, colloid cancer, of leather-bottle type. In such doubtful cases a relatively benign course and the combination of quite good health with a large stomach lesion (often shown best by the *x*-ray) always suggests syphilis.

Occasionally at operation the appearance of a hard, well-defined, plaque-like lesion, or a dense, nodular tumor arising from a diffusely infiltrated stomach wall, together with the serum reaction, may strongly suggest syphilis.

The diagnosis of syphilis of the stomach has not been and will not be absolute as a rule. Few autopsies occur, the surgeon tends to avoid operation and especially the resection of tumors in patients with strong positive Wassermann reaction, and, finally, the diagnosis usually cannot be made at operation. No doubt a considerable number of syphilitic stomach tumors have been treated surgically in the past without recognizing their syphilitic nature.

The remainder of the cases with definite lesion in the stomach fall into two groups, according to the character of the lesion found: Class A, chronic ulcer type, and Class B, chronic indurative or gummatous type.

There were 5 cases in Class A, with chronic ulcers involving the pylorus, antrum, or lesser curvature of the stomach, and one median ulcer with adhesion causing an hour-glass deformity. In 1 case there were three ulcers. There was obstruction of the pylorus in 3 cases and gastro-enterostomy was performed in these, also in the hour-glass stomach.

In Class B were 2 cases, one with leather-bottle induration of the whole stomach, one with gumma in the antrum the size of a large plum; the pylorus was not obstructed in either.

Taking these two groups of seven patients together the ages were twenty-three to sixty-three and averaged forty-four years. The patients were all in the tertiary stage. The digestive disturbance appeared from eight to twenty-four years after the initial lesion, in the 5 cases where this was determined. Six cases had had some antispecific treatment but in only one had it been thorough. The Wassermann was triple positive in all. The duration of all gastric symptoms averaged five years, and of the present gastric disturbance, eight months.

The symptoms consisted of distress, pain or soreness in the epigastrium with irregular vomiting, often distress on the empty stomach, relieved by food or alkalies, resembling much the irregular course of recurrent gastric ulcer; later the distress or pain was more constant.

In the five ulcer type cases the free HCl averaged 25, with minimum of 8 and maximum of 40; the total acid averaged 46, with minimum of 15 and maximum of 70; 4 cases showed twelve-hour retention of food.

The other 2 cases (Class B) showed no free HCl in the gastric contents and a total acidity of 14 and 16. There was no twelve-hour food retention.

Occult blood was found by the benzidin test in stomach contents and stools in 2 cases. The *x*-ray was very valuable in giving the shape, size, and position of the lesions. The contour in Class A

was exactly that of chronic peptic ulcer, with its complications (obstruction, hour-glass), and in Class B of cancer, of the scirrhous or medullary type.

Frequency and Relation to Peptic Ulcer. It is very difficult to judge the frequency of syphilis of the stomach. Some regard every dyspepsia in a syphilitic as a sign of syphilitic gastritis. It seems far more likely that these dyspeptic symptoms do not arise from gastric *lesions*, but accompany the primary disease, as dyspepsia in tuberculosis is not due to any form of tubercular lesion of the stomach but to the toxemia.

Actual syphilis of the stomach is evidently one of the rarest types of syphilis. It is certainly striking that in a large hospital like the Boston City Hospital, admitting daily to its wards one or two patients with a triple positive Wassermann reaction, that so very few are found to have any organic lesion of the stomach, including possible coincident lesions. This agrees with the autopsy figures of Chiari and the later figures of Symmers, who found in 314 autopsies in syphilis only one genuine syphilitic ulcer of the stomach.

Syphilis was formerly looked upon as an important cause of chronic gastric ulcer. Lang and Neumann judged about 20 per cent. of gastric ulcer syphilitic, and Engel about 10 per cent. This is disproved by serum tests. Syphilis is a rare cause of ulcer. In less than 0.5 per cent. of 179 private cases of proved peptic ulcer was the Wassermann positive and in less than 2 per cent. of 204 hospital cases. It must be remembered that this figure for peptic ulcer in hospital patients is distinctly less than the percentage of syphilis in the total hospital cases, which is at least four or five. Smithies found a positive Wassermann reaction in 0.33 per cent. of a series of proved ulcer cases.

It has been impossible to decide whether the cases of chronic ulcer type (Class A) had a syphilitic or coincident ulcer of the stomach. This is true of some of the cases recently reported by Downes and LeWald. No spirochetes were found in glands and stomach tissue resected in two of our cases.

Chronic ulcer and syphilis are both common; they may be coincident without relation in at least a portion of the few cases found. An ordinary peptic ulcer may occur in syphilis with the

same frequency at least as in other persons. An ulcer in a luetic may improve under treatment without proving it a syphilitic ulcer.

On the other hand the recent work of Warthin and others suggests that in the active stages of syphilis there is a spirochetosis of all the viscera, and that every syphilitic has patches of fibrosis scattered through the tissues as has been proved in the heart, aorta, pancreas, etc. The stomach may be involved in such a process and fine syphilitic lesions be later proved more frequent than they appear now.

Symptoms. There are no characteristic symptoms of syphilis of the stomach, as is seen in the summary given of these cases. There is usually a long history of intermittent symptoms, later becoming more constant. They sometimes resemble those of chronic catarrh, or ulcer, or growth, with or without obstruction of the pylorus. Pain is common; gross hemorrhage is infrequent possibly because of obliterative endarteritis. It is useless to try to classify cases strictly on the basis of symptoms. There is usually much longer duration of symptoms and less cachexia and loss of weight in proportion to the size of tumor than in cancer. They behave like benign not malignant lesions. It is a disease of middle life; the age is below the average for cancer.

It is evident that stomach symptoms in tertiary syphilis are rarely the expression of a gumma or ulcer. Brugsch and Schneider suggest that they may be largely due to the irritation of spinal nerve roots similar to the crises of tabes but more latent. Changes in the abdominal aorta may give local pain and tenderness.

Signs. In the cases without organic lesion of the stomach the gastric secretion has proved normal in the majority and below or absent in one case in five. This is quite different from Neugebauer's figure in the secondary stage of syphilis, namely, 62 per cent. subacidity and 18 per cent. achylia.

Brugsch and Schneider have stated that an ulcer in tertiary syphilis is usually associated with subacidity or achylia. On the contrary, we found normal or increased secretion in little more than half our cases of ulcer type, perhaps, because the majority had pyloric obstruction. Our data agree with those of Smithies in a larger series. The 2 cases of indurative gumma type (Class B)

had no free HCl. In reporting secretion we must always take account of stenosis and the age of the patient. In obstructive cases the food is long retained and the added stimulus gives normal or increased secretion. In others the stomach empties so fast after the test meal that there is little chance for the stimulus of food to develop HCl. The reduced acidity is probably not mechanical alone, a systemic disease like syphilis influences gastric chemistry in more than local ways.

Occult blood was found in gastric contents or stools in 2 cases. Palpable tumor was found in 1 case only.

Diagnosis. The literature is large and indefinite and case reports before 1910 not including the Wassermann test and the *x*-ray have minor value. In the older cases the diagnosis was often accidental and made only at autopsy or operation, or as the result of a random therapeutic test.

The difficulties of diagnosis have been sufficiently emphasized between syphilitic lesions and peptic ulcer or cancer. We cannot depend on symptoms, on changes in secretion, on the contour or site of the lesion, or its appearance at operation. Ulcer is an anatomical not an etiological diagnosis. The combination of ulcer and anacidity does not favor syphilis more than it does cancer.

Even the relief of symptoms by treatment is not a sure guide in diagnosis, though, if plaques, large indurated areas, hour-glass deformity, tumors, easily demonstrated by *x*-ray or operation on a patient with positive Wassermann have previously resisted treatment and fade away under drugs, we have valuable evidence that the lesion was specific. While the clinical picture does not differ from other lesions, the results of treatment usually do. In doubtful abdominal cases think of syphilis.

The *x*-ray has proved of great value in locating the lesions exactly and following their changes under treatment accurately. We no longer need depend on the palpation of a rare tumor and its disappearance under the finger.

Prognosis. *Results of Treatment.* The prognosis is about that of syphilis in general. The results of treatment are usually prompt and striking; the majority improve, even cases with severe complications like stenosis, perforation, and hemorrhage. A good portion

are cured, but a small group do badly in spite of thorough treatment. Gummata and induration melt away but scar tissue does not dissolve and some deformity usually persists in the cases with gastric lesions. Gastric secretion may remain absent after symptoms have disappeared.

In the 37 cases without definite stomach lesion, 16 (43 per cent.) are well; 18 (48 per cent.) improved and 3 (9 per cent.) no better.

In our 7 cases with stomach lesions (omitting the 2 cancer cases) 3 (43 per cent.) are well, and 4 (57 per cent.) greatly improved. In this group there were gains in weight of 15 to 52 pounds with an average gain of 31 pounds.

The prognosis was called "extremely good" in summaries of older reported cases. This may be due to the use of the therapeutic test in diagnosis, since only cases which improved rapidly were considered syphilis. Some caution must be used in prognosis since in spite of the remarkable results in individual cases, less than one-half the patients were wholly freed from dyspeptic symptoms.

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PERICARDIOTOMY FOR SUPPURATIVE PERICARDITIS FOLLOWING PNEUMONIA

By C. N. B. CAMAC, M.D.
AND
E. H. POOL, M.D.
NEW YORK

Operative intervention in wounds of the heart and pericardium has become so successful in recent years that it is reasonable to hope that surgery may be employed more frequently and more successfully in non-traumatic suppurative pericarditis. In order to stimulate discussion on this topic we present this report.

In a series of papers by American writers, Roberts, 1897, Porter, 1900, Eliot, 1909, and Rhodes, 1915, there has appeared an exhaustive presentation of the subject of suppurative pericarditis, with a collection of the reported cases of pericardiotomy for suppurative pericarditis. "The cases numbered 86, of which 45 recovered and 41 died, a percentage of 52.3 recoveries against 47.7 deaths. In the complete series the infecting organism is reported in but 21, the pneumococcus was found in 9 cases, staphylococci in 4, streptococci in 2, the colon bacillus in 1, the Bacillus pyocyaneus in 1, and a 'double coccus' in 1" (Rhodes).

In connection with the case here presented, a case of pericardiotomy for suppurative pericarditis following pneumonia and empyema, we present synopses of the reports of similar cases. We also revised the details of the technic of paracentesis pericardii and pericardiotomy.

Case Report.—Patient, male; aged forty-seven years; occupation, engineer. Family and past history negative. Patient had been under the care of one of us (Camac) for various illnesses for the last fifteen years. These illnesses had no bearing upon the present attack. On December 24,

1915, at the office of one of us (Camac) patient was seen for a furuncle on the back of the neck, which was opened and dressed. On the 29th the wound was practically healed.

On December 30 the patient was seen at his house, and complained of a slight pain in the lower right axilla, on taking a deep breath. Examination showed a few very fine, almost inaudible crepitant rales at the right base, with somewhat harsh, vesicular breathing. Temperature, 104°. He was flushed and felt ill. Respirations, 34; pulse, 105. He was put to bed and preparations made for possible pneumonia, which on the next day, December 31, gave frank signs at the lower right lobe. The blood count showed hemoglobin, 85 per cent.; red blood cells, 4,900,000; white blood cells, 10,000. The differential count showed 85 per cent. polynuclears. Urine showed a specific gravity of 1.031, otherwise negative. The temperature ranged between 104° and 105° for two days, falling to between 102° and 104° on the following two days, remaining at 102° with one slight rise, for the following four days.

On January 8, the twelfth day of the disease, it was noted that the tubular quality of inspiration and expiration was more intense along a transverse line at the level of the angle of the scapula, with a diminishing intensity toward the base of the lung. An exploratory puncture on this date revealed a thin, purulent exudate. Thoracotomy and drainage was performed immediately by one of us (Pool). Cultures from this exudate yielded Staphylococcus pyogenes aureus, from which vaccines were prepared. Patient did well for the next eight days, temperature gradually falling to 99.3°. On January 10 the following note was made. "Heart action strong and regular, no dropped beats. The rhythm is clock-like, there being no rest periods." On January 11 the following nurse's note: "Respirations labored most of the day. Pulse feeble and intermittent. Breathing better upon loosening dressing." January 15 and 16 showed a distinct change in pulse, somewhat irregular and weaker. On the 16th the color of the skin was noted as bad, and the respirations labored. Physical signs suggested pericardial effusion, which was confirmed by exploratory puncture; a thin, purulent exudate being obtained, which, on culture (by Dr. Mortimer Warren) revealed the same organism as that found in the pleura. The opening and draining of the pericardium was now considered as offering the only chance of relieving the severe cardiac embarrassment. This was done under local anesthesia by one of us (Pool) by the method described in the discussion following this report. While the patient's condition was critical during the operation, his color and pulse improved markedly the moment the pericardium was relieved of the purulent effusion. He continued to do well for six days following the operation; the pulse, however, being somewhat irregular and at no time forcible. The respirations occasionally became labored, but were always relieved after dressing the pericardial wound. On January 22 the calf of the right leg became painful and swollen,

and it was evident on examination that phlebitis had developed. Blood culture at this time showed Staphylococcus aureus. On the evening of the 22d the heart action and breathing became greatly embarrassed, and the following note was made: "Temperature has steadily risen since operation; pulse weak; no heart sounds audible; drainage poor. Digital examination of the wound showed heart sealed to pericardium. Finger introduced deeply in wound, and fresh adhesions broken up, yielding a copious discharge of very thick stringy material and much pus. Patient's condition markedly improved and the heart sounds became distinctly audible." On the 23d and 24th respiration and heart action remained good, and the drainage from the pericardium free. On the 26th the pulse became small and intermittent, and there was considerable nausea. On the 27th the temperature reached $104\frac{2}{5}°$, falling to 102° on the 28th. On this date the chest was radiographed. The report of the findings is as follows:

Indications of fluid and some air in the right pleural sac, with partial collapse of the lung. The heart shadow is distinctly enlarged, suggesting fluid in the pericardium.

Autogenous vaccines were employed, but it was realized that these were used too late in the disease to markedly influence its course. On January 29 the patient died.

Paracentesis Pericardii as a Diagnostic Adjuvant.[1] Although this procedure exposes to the danger of accidental injury to the heart, coronary artery or vein, pleura, lung or internal mammary artery, it must be emphasized that serious accidents have occurred so infrequently that there should be no hesitancy in performing paracentesis when the operation seems definitely indicated. The limitations of exploratory puncture should be definitely appreciated. Even when fluid is present, puncture has often proved unsuccessful. A dry tap may result from the needle becoming blocked with fibrin or with tissue that has been penetrated during its introduction. Moreover, the exudate, especially early, may lie in such a position as to be out of reach of the needle. If suppurative pericarditis is suspected, diagnostic punctures should not be made repeatedly; when several attempts have been made, puncture should be abandoned in favor of pericardiotomy. It must be stated that a number of writers decry the use of puncture for diagnostic purposes. Rhodes states that it can be of positive danger and is usually superfluous.[1]

[1] Some parts of this article are taken, with permission of the publishers, from Johnson's Operative Therapeusis: Heart and Pericardium, by E. H. Pool, published by D. Appleton & Co.

Opinions differ widely as to the point of election in paracentesis of the pericardium. The favorite sites for puncture fall into two groups: those which are planned to avoid the pleura and those which disregard the pleura, but are planned to avoid the heart. Under normal conditions the pleura can be avoided by introducing the needle in the region of the sixth and seventh cartilages of the left side, close to the sternum, or below the tip of the xiphoid. On the other hand, cardiac injury is best avoided by puncture at a point somewhat internal to the lower part of the left limit of pericardial dulness. Curschman advocates this site in preference to one in the immediate vicinity of the cardiac margin or apex because the effusion is very frequently associated with an enlarged heart, in which case the heart may extend beyond the apparent position of the apex; moreover, it is at times adherent to parietal pericardium. The disadvantage of the outer site is that the pleural cavity may be entered, a feature which is especially disadvantageous in the presence of suppurative pericarditis, but penetration of the pleural cavity is not a necessary complication, because the pleural edges are separated by the distended pericardium and not infrequently the pleural layers are agglutinated to a considerable degree by adhesions, causing obliteration of the anterior part of the pleural sac.

The following sites are most suitable for paracentesis of the pericardium:

1. A point slightly internal to the left limit of dulness, in the fifth or sixth intercostal space.

2. Midline immediately below the xiphoid process. This situation is recommended by François, and others, as the point of election because here the pericardium is reached by the shortest route, without injury to bloodvessels, pleura, or peritoneum; while the exudate can be evacuated before the heart is touched. The only contraindications of this method are extreme malformations of the sternum and a high degree of tympanites. Under local anesthesia, a fine trocar or needle is inserted and pushed directly upward to a distance of 2 cm., along the posterior surface of the xiphoid. In this way the peritoneum is avoided, and after passing through the diaphragm, the point of the needle is directed upward and backward.

3. A point in the angle formed by the base of the xiphoid process and the seventh left cartilage at its insertion. The choice between these sites must depend upon individual indications.

Pericarditis occurs as a relatively frequent complication in a large number of diseases, the most frequent of which are inflammatory rheumatism, nephritis, pleurisy, pneumonia, pyogenic infections, and tuberculosis, but there are "few infectious diseases which may not implicate the pericardium" (MacPhedran).

The clinical picture of pericarditis with effusion is variable. Besides the local objective signs, the cardinal sign of exudative pericarditis being a characteristic cardiac dulness which is at first increased upward, there are present to a variable degree, symptoms due to: (1) involvement of the heart muscle (myocarditis), which is the most frequent and serious lesion; (2) endocarditis (these two are especially frequent in association with rheumatism); (3) mechanical disturbance of the heart as a result of pressure exerted by the effusion; this, however, is infrequent; (4) general constitutional disturbances, depending upon the type of the infection, the pericardium offering a large surface for absorbtion; (5) an associated lesion or disease.

Suppurative pericarditis represents an abscess corresponding to a part or the whole of the pericardial sac. The most frequent organisms are the streptococcus, staphylococcus, and pneumococcus. The exudate is usually purulent from the beginning of the attack, although occasionally it develops in the course of a non-suppurative pericarditis. As a rule purulent pericarditis is secondary in the course of a pyogenic infection, and under such conditions it frequently constitutes a "terminal infection;" in rare cases suppurative pericarditis is primary; in some cases the infection is introduced through a wound.

Suppurative pericarditis is characterized by the local signs of pericarditis with effusion and constitutional symptoms of a septic character. The fact that the pericarditis is frequently a secondary lesion causes its presence to be overlooked in many cases. In children the symptoms of pericarditis are particularly apt to be masked. On the other hand, in many cases where the lesion has been recognized and the pericardium drained, the operation has

been unsuccessful because a coexisting purulent focus, especially empyema, has been overlooked. It follows that in septic processes it is necessary to watch for the development of pericarditis; moreover, the recognition of such a condition should not cause less thoroughness in the search for other foci.

The distribution of the fluid in the distended sac must be understood in order to appreciate the technical details of paracentesis or pericardiotomy. First, the recesses become filled, the fluid gathering chiefly in the region of the base of the heart; then the bulging pericardium, confined anteriorly, separates the yielding lungs and pushes the diaphragm downward. The increasing exudate progressively distends the pericardium, for the most part to the left and posteriorly. It must be emphasized that the heart usually, though not invariably, occupies a low position and remains applied to the anterior wall of the thorax. Occasionally an inflammatory process may become localized by the formation of adhesions and the limitation of the exudate to a circumscribed part of the sac.

Pericardiotomy. The methods of pericardiotomy may be divided for convenience into two groups:

1. Procedures which reach the pericardium through the thoracic wall.

2. Procedures which enter from below the costal arch, the epigastric route.

The first method of procedure includes:

Resection of the sixth cartilage, as recommended by Kocher, Axhausen and Pels-Leusden.

Resection of the fifth cartilage, Gussenbauer and Ollier.

Resection of fifth and sixth cartilages, Delmore and Mignon.

The second method of procedure has been accorded the preference by Larrey, Mintz, L. Rehn, and Allingham. The approach is in part or entirely from below the costal arch, and is both extrapleural and extraperitoneal.

Pericardiotomy for the Evacuation of a Purulent Exudate. In the treatment of suppurative pericarditis the method of pericardiotomy to be efficient must provide for satisfactory drainage, and be sufficiently simple to be rapidly performed under local anesthesia if necessary. Adequate drainage is the essential feature,

and upon this must depend, to a large extent, the choice of method. In the interest of good drainage it is important, (1) to open the pericardium at its lowest point and (2) to provide such an opening as will ensure ready egress for an accumulation of fluid in both the right and left spaces of the pericardial sac. Local anesthesia is frequently imperative because the heart is apt to be dilated and insufficient as a result of endocarditis and myocarditis. It is necessary that the work be done with the least possible associated injury. It is not sufficient to avoid wounding the heart; if possible, the heart should not be touched. Further, thorough anesthetization of the pericardium is advisable on the basis of significant experimental work, which we will briefly summarize.

Serious disturbances of the heart action have been noted repeatedly to result from irritation of the pericardium. Heitler's observations on dogs showed that irregularity of the heart follows mechanical or electrical stimulation of the pericardium. D'Agata (1912) in animal experiments found that a sudden drop in the blood-pressure occurred as a result of grasping and incising the pericardium. These phenomena are presumably reflex in character; they help to explain analogous clinical observations. Thus, Harrigan reported temporary arrest of the heart upon incision of the pericardium in a case of suppurative pericarditis.

Heitler and D'Agata found in their experiments that preliminary cocainization of the parietal layer of the pericardium prevented the occurrence of irregularity of the heart and the lowering of the blood-pressure. Heitler recommended that before an incision is made in the pericardium, it should be anesthetized by means of a 10 per cent. solution of cocain applied to its surface. Presumably novocain by injection could be substituted to advantage in man.

The two methods most appropriate for drainage in suppurative pericarditis will be described in detail.

1. Resection of the sixth costal cartilage (Kocher).

2. Resection of the seventh, or sixth and seventh costal cartilages (Rehn).

Resection of Sixth Cartilage. This method affords adequate drainage at a dependent part of the sac, is simple and quick of execution, may be performed readily under local anesthesia, and the

exposure may be extended easily in any direction. It appears the best method for general use and was the method employed in our case.

With the patient in a semirecumbent position, an incision is made in the course of the sixth cartilage and rib, passing from the midline obliquely outward. The perichondrium is incised in the direction of the wound and separated. The cartilage is then severed close to the sternum and lifted, the perichondrium being separated from its posterior surface. The cartilage is broken at its junction with the rib and removed. The internal mammary artery should be divided between ligatures when exposed. The triangularis sterni is then split. An effort should be made to identify the anterior edge of the underlying pleura, which should be pushed outward. The pericardium is thus exposed. It should be grasped and lifted with two pairs of toothed forceps and incised. (The importance of anesthetizing the pericardium has been emphasized above.) The pericardial incision is extended with blunt-pointed scissors. The pus should be allowed to escape slowly. A finger is then introduced to break up adhesions and to evacuate walled-off accumulations of pus. Should the access be too small to allow separation of adhesions or for adequate drainage, the opening may be enlarged in an appropriate direction, by resection of part of the sternum, excision of part of the sixth rib, or removal of the fifth or the seventh costal cartilages. Residual fluid should be removed by aspiration, as in abdominal operations, and sponging or wiping of the serous surfaces should be reduced to a minimum. Clots of fibrin should be extracted with forceps. Irrigation with sterile salt solution has been used for the removal of clots of fibrin, but is not to be recommended. The use of antiseptic fluids is contra-indicated. In closing the wound it is advisable, especially if the pericardium is considerably separated from the sternum, to suture it to the skin. This not only facilitates drainage but "diminishes the risk of contamination of the anterior mediastinum" (Eliot).

Drainage is favored by the movements of the heart which, in the absence of adhesions, tend to force out any accumulated pus (Eliot). The kind of drain which should be used is a detail which demands some discussion. The choice lies between a rubber tube and soft

drain. Tubes afford the most satisfactory drainage and may be sutured to the soft parts so that they are not readily displaced. But if the tube should come into contact with the heart it is likely to interfere with the cardiac action, as occurred in a case operated upon by Riedel. Rehn recommends 2 rubber tubes, 1 passing to the right side and 1 to the left to drain both pockets. Eliot, Riedel and others favor soft drains. A general rule cannot be made; the mode of drainage must be such as to fit the individual case. Two cigarette drains were employed in our case. They did not drain satisfactorily. We are of the opinion that split soft-rubber tubes would have been better.

The sitting position should be enforced in the after-treatment as most favorable for drainage. The wound heals, as a rule, without a persistent sinus and "after healing is complete, insufficient or irregular heart action is the marked exception, neither is there any indication of cardiac displacement" (Eliot).

Resection of the Seventh, or Sixth and Seventh Costal Cartilages. A curved incision of about 6 cm. is made along the lower margin of the seventh left cartilage to the base of the ensiform process, across which the incision is continued transversely. The incision is deepened and the seventh costal cartilage divided. The internal mammary artery is preserved. Detaching the soft parts, the finger is passed under the sternum, between the lower portions of the triangularis sterni muscle and the sternal portions of the diaphragm. A piece of the sternum and seventh costal cartilage is removed, followed by resection of the sixth costal cartilage, if necessary. The pericardium is readily reached without opening the pleura. The more distended the pericardium the easier the operation. (Description after Küttner.)

Prognosis. Suppurative pericarditis demands immediate incision and drainage. The prognosis in purulent pericarditis is in general unfavorable, yet in suppurative processes which are confined to the pericardium early operation is quite often followed by recovery; on the other hand, where the pericardium is involved secondarily in the course of a general sepsis, recovery is infrequent. Nevertheless, cases that appear hopeless are occasionally saved by operation. As mentioned below, a prognosis should depend largely

on the characteristics of the organism causing the disease, but as yet this feature has not been studied with sufficient accuracy to consider it in this report.

Conclusion. The results of pericardiotomy are necessarily modified by the gravity of the fundamental disease, but striking cures have followed operation in apparently hopeless cases of severe infection. In studying our case, together with the literature here quoted, the need for a bacteriological division of these cases seems imperative. From Rufus Cole's work we now have a new aspect of the clinical condition known as pneumonia. This new viewpoint is bacteriological in character. We now know that the anatomical diagnosis of consolidation of a lobe, or of a purulent accumulation in the pleura or pericardium may be correct, and yet the clinical course vastly different, according to the organism producing the condition. In traumatic injuries to the pericardium where operation has been successfully performed and recovery has followed, the favorable factor is usually the absence of infection. In our case a virulent organism, staphylococcus, was the cause of a bacteriemia. Was the dose and virulence of the toxin so overwhelming that no known method would have been sufficient to overcome them? Perhaps vaccines should have been used from the time of the furunculosis, but at that time no culture was taken and there was prompt recovery from the single abscess in the neck. The question naturally arises as to whether we should regard such simple abscesses as demanding immediate vaccine treatment as a routine, in view of the possibility of the development of larger areas of pus in more vital localities. As to the justification for pericardiotomy in all cases of suppurative pericarditis, it would seem that the operation should be performed as an emergency procedure, even in desperate cases. The importance of an early diagnosis cannot be too strongly urged, whether exploratory puncture reveals a purulent or a non-purulent effusion, cultures should be made and an accurate report presented. We may expect that further bacteriological studies will throw light upon the general clinical course due to different types of organisms. Thus the prognosis in a given case may be made more exact and the indications for surgical intervention may be further developed. This case, and those quoted from the literature go to

emphasize the fact now being grasped by the profession that pneumonia is a local manifestation of a systemic infection, and in dealing successfully with it measures capable of reaching the antigen power of the system must be sought and employed.

THE FOLLOWING COLLECTED CASES ARE ARRANGED AS FOLLOWS:

Suppurative Pericarditis following: (1) Pneumonia; (*a*) Lobar; (*b*) Broncho. (2) Empyema.

A bacteriological division is not possible, as cases have not been studied accurately with this feature especially considered. This is a most important aspect of suppurative pericarditis and offers a field for future investigation. From the data in some reports it is difficult to determine whether pneumonia was clinically present.

1. Pneumonia: (*a*) Lobar.

Tallquist (cf. Rhodes): Finska laksallsk. Handl., Helsingfors I, 1912, 575–595.

Female, aged forty years. Croupous pneumonia, empyema, and purulent pericarditis. Thoracotomy for empyema; six days later pericardiotomy, Ollier's method. Fifth rib resected. Pericardium opened 400 to 450 c.c. of pus with fibrinopurulent exudate evacuated. Drainage tube introduced and held by suture. After operation patient in collapse and cyanotic. Gradual recovery. (Original article not accessible.)

Mintz-Chirurgia, April, 1912, vol. xxxi (Russian). Centralblatt f. Chir., 1912, No. 30, p. 1046.

Boy, aged twelve years. Bilateral diplococcus pneumonia. Ill for about two weeks, and was in bad condition before the operation, heart dulness extending two fingers' breadth beyond the right sternal margin and to the midaxillary line on the left side. Incision along the lower margin of the seventh costal cartilage. A skin and cartilage flap formed, which was turned upward, permitting access to the space through which the pericardium could be opened without injuring the pleura; 100 c.c. of seropurulent fluid was evacuated, and a tampon introduced. General condition continued to improve; patient discharged after about two months, with normal heart boundaries, and without any disturbance, except a fistula from which a small amount of pus escaped.

Strauss: Nuremberg Med. Soc., meeting of July 15, 1909, Münch. med. Wchnschr., 1909, No. 39, p. 2039 (or 7).

Boy, aged five years. Bilateral croupous pneumonia. Apex beat could not be felt; the heart sounds were very faintly audible. Dulness two fingers' breadth beyond the right sternal margin and a finger's breadth beyond the nipple-line to the left side. Exploratory puncture in the fifth intercostal space yielded 60 cm. of thick fluid pus, and was followed by visible improve-

ment. Pericardiotomy, with resection of the fifth costal cartilage, according to Ollier. Half-liter of pus escaped. The heart was found lying behind and above, floating free in the large cavity. Subperichondral resection of the fourth costal cartilage was added. Drainage with rubber tube, thickness of thumb. In three weeks cavity had entirely disappeared, without leaving a thoracic deformity. Good recovery.

The author emphasizes the advantages of pericardiotomy with costal resection, on the basis of Terrier's statistics, and recommends early operative interference, which has a simple technic as in empyema and yields the best results as to life and rapid healing.

Blake: New York Surgical Society, October 28, 1908; Annals of Surgery, 1909, xlix, 142.

Pericarditis secondary to double pneumonia. The pericardium was opened in the midaxillary line and a large amount of pus was evacuated. A few days after the operation there were signs of pus farther back, and an incision there revealed an empyema. The patient died.

Walzel: Mittlg. a. d. Grenzbeg. d. Med. u. Chir., 1913, xxv, 264.

Boy, aged nine years. Left-sided pneumonia. On the ninth day dulness was noted, extending on right side one finger's breadth beyond right sternal margin; on left side two fingers' breadth beyond the left maxillary line. Heart sounds inaudible; superficial veins of thorax much distended, especially on right toward shoulder. Pericardiotomy was performed by v. Eiselsberg, in spite of the patient's apparently moribund condition. Resection of fifth costal cartilage. Exploratory puncture of bulging pericardial sac yielded pus. Transverse incision of pericardium; escape of about one liter of thick yellow pus. Two rubber drainage tubes. Pulse was plainly palpable three hours after operation. General condition rapidly improved. A fistula persisted for nine weeks. Recovery. Bacteriological examination of the pus showed streptococci. The patient was reëxamined nine years after operation, and was found to be in good condition.

Pandlebury (cf. Eliot): Lancet, October 22, 1904, p. 1144.

Man, aged thirty-one years. Pneumonia chiefly involving the left lung. Three weeks later cardiac dulness four fingers' breadth to the right of the sternum, with muffled heart sounds, persistent high temperature, considerable cyanosis and dyspnea. Pericardium was incised, after removal of the seventh costal cartilage and a portion of the sixth; 3 or 4 ounces of fluid were withdrawn. Numerous adhesions between the right heart and parietal pericardium were broken down, and a tube was inserted, which was removed on the sixth day after the operation. The patient made a good recovery.

Scott (Eliot): New York Med. Jour., January 30, 1904, p. 198.

Male, aged thirty-six years. Bilateral pneumonia. On thirteenth day the pericardium was considered involved. Twenty-first day, the cardiac

dulness was decidedly increased in all directions, especially toward the right. Exploratory puncture yielded a turbid greenish fluid. On culture a pure growth of pneumococci. Incision of pericardium and evacuation of about a pint of pus. Examination showed pneumococci. Drainage tube removed twenty-six days after operation, and the patient left the hospital fifty-one days after operation, free from physical signs of an adhesive pericarditis.

Hall (Eliot): Lancet, 1903, ii, 951.

Woman, aged thirty-eight years. Puerperal sepsis and double pneumonia, three weeks before admission to the hospital. Extensive area of cardiac dulness, the heart sounds being almost inaudible. Puncture of the pericardium in the fourth intercostal space yielded pus. Excision of the fourth left costal cartilage with evacuation of 20 ounces of grayish-yellow pus. Drainage, with profuse discharge, until death one week after the operation, probably due to suppurative peritonitis.

Examination of the pus from the pericardium showed various streptococci and staphylococci.

Coutts and Rowlands (Eliot): British Medical Journal, 1904, i, 9.

Patient aged two and a half years. Pneumonia a month before admission to the hospital, when the diagnosis was made of a probable empyema at the right base, with a purulent pericarditis. Chloroform anesthesia. Oblique incision exposing fifth left cartilage which was removed in part with adjacent part of sternum. Incision of the pericardium with evacuation of about half a pint of thin greenish-yellow pus under pressure. A rubber drainage tube was inserted. Pericardial fluid contained a coccus which resembled pneumococcus. Temporary improvement. The empyema pus, obtained by operation on next day, showed a coccus which resembled the pneumococcus; other forms of cocci and bacilli were also numerous. The patient died in the sixteenth week after the operations.

Necropsy. On opening the thorax there was found a condition of universal dense adhesion of the contained viscera to each other and to the chest wall, and the whole anterior mediastinum was occupied by a thick fibrogelatinous deposit. The wound over the pericardial area drained a small pocket on the anterior surface of the heart, but elsewhere the pericardium was inseparably adherent to the heart in front. On attempting to separate the pericardium from the left lung an abscess cavity was opened, with a discharge of 3 ounces of pale thick pus. This cavity lay behind, and to the left of the heart and within the pericardial sac; its walls were very thick from the presence of fibrinous matter similar to that occupying the mediastinum. Between the heart and the right lung there lay another smaller cavity, independent of the first, and full of inspissated pus. The pus in both cavities was dry and gritty to the feel, as if impregnated with lime salts. The tracheal glands were greatly enlarged, but free from all sign of tubercle. The pleuræ were everywhere adherent.

Sibley, Arbuthnot Land and Rowell (Eliot): British Med. Jour., May 23, 1903, p. 1192.

Boy, aged sixteen years; sore throat, followed a day or two later by most of the symptoms of pneumonia of the left base without very distinct physical signs. At the end of three weeks a left empyema was opened, without much relief to the general symptoms. Ten days afterward the pericardium was opened, with only slight temporary general improvement. Death thirteen days after incision of pericardium, apparently due to external hemorrhage from the heart through rupture of a small parietal abscess.

Bacteriological examination proved the presence of pneumococci in great numbers in the blood, death being the result of a general pneumococcus pyemia.

Connor, L. A. (operator, Stimson): Medical News, January 20, 1900, lxxvi, 115. New York Academy of Medicine, stated meeting, December 19, 1899.

Pericarditis developed after a severe (left-sided) pneumonia. Aspiration showed the presence of a purulent effusion. Thirty ounces of the fluid were removed by aspiration. Pericardiotomy under local anesthesia, nearly 40 ounces evacuated. The pleura was slightly incised at the operation, and probably became infected, although it was at once carefully closed. The patient's condition at once improved and the alarming acute symptoms disappeared. The right pleura extended beyond the sternum, owing to the compensatory hypertrophy of the right lung, because of the pneumonia in the left. The accidental incision of pleura probably followed by infection. Patient died of purulent pneumonia a few days later.

Lilienthal, H.: Medical News, 1899, lxxv, 697. Presentation of case, New York Academy of Medicine, Section on Surgery, November 13, 1899.

Male, aged fifteen years. Severe double lobar pneumonia. Pericardial friction sound heard on the fourteenth day. No increase of heart dulness could be demonstrated for two days, however. Ten days later the patient was in very bad condition and was aspirated for the pericarditis, with removal of 18½ ounces of pus. This was found to contain a pure culture of the pneumococcus. No improvement. Operation under local anesthesia, incision from third to fifth intercostal space; resection of three-quarters of an inch of the costal cartilages. Penetration of pericardium was at once followed by a tremendous gust of pus, estimated at 50 to 60 ounces. Wound was left open; no artificial drainage. Irrigations with normal salt solution. Patient in excellent general condition three months after the operation. Bacteriological examination showed pneumococcus in pus in pure culture; pneumococcus and streptococcus in sputum.

Ljunggren, C. A.: Nord. Med. Arkiv., 1898, ix, 1.

Male, aged twenty-four years. Lobar pneumonia. Sudden attack of chills and fever; followed by dyspnea and pain in left half of chest. Exploratory puncture. Incision in middle of fifth intercostal space, between ster-

num and nipple. Incision showed the existence of pleural adhesions. The pericardium opened, and a large stream of pus spurted out. Patient was in collapse, but recovered after digital massage of the heart. The fluid had a greenish color, contained some fibrin flakes, and amounted to about 1½ liters. A thick, long drainage tube was inserted, reaching to the back portion of the pericardium. After a fortnight careful irrigations of the pericardial cavity with salt solution were begun and repeated every third day, to wash away the fibrin coagula, but it finally became necessary to do a resection of the fifth rib, in order to obtain a freer access to the pericardium and break up adhesions. After this, recovery was rapid; fistula closed a month later. Patient discharged in good condition about five months after admission to the hospital.

No bacteriological growth from original fluid; microscope showed small, short bacilli often lying two or three together. Bacillus pyocyaneus grew in all cultures made from the discharge after operation.

Sevestre, R.: Lancet, April 23, 1898, i, 1109.

Male, aged twenty-two years. Acute pneumonia. Pericardiocentesis; incision in fourth left interspace, under cocain. Forty-five ounces of pus escaped. Irrigation with boracic acid. Tube drain. Temporary improvement was followed by purulent effusion in both pleural cavities. Bilateral costal resection, and escape of 35 ounces of pus. Pneumococci were present in the pus from both pleural cavities. The pus from the pericardium showed almost a pure culture of pneumococci. Death one month after admission to the hospital.

Bradbury, quoted by Sevestre: Lancet, 1898, i, 1111.

Male, aged twenty-two years. Purulent pericarditis due to pneumonia. No pericardial friction. Double empyema. Aspiration fourth space one inch from sternum; incision in same place. Evacuation of large amount of pus. Death eighteen days after operation. Autopsy findings: Thickened pericardium; double empyema.

West, S.: British Medical Journal, December 8, 1883, p. 1129; February 21, 1891, p. 404.

Boy, aged fourteen years. Pleuritis, pneumonia. Abscess of thigh, acute arthritis of left shoulder. There was much dyspnea and some cyanosis, and there were physical signs of pneumonia of the base. The left pleura was tapped, but only a few ounces of serum were evacuated; from the pericardium 24 ounces of pus was drawn off. Though relieved for a time the dyspnea and cyanosis returned, and the patient died.

Davidson, P.: British Med. Jour., March 14, 1891, p. 578.

Boy, aged six years. Pyemia and septic pneumonia after necrosis of metatarsus. Pus having been shown by aspiration, the fifth interspace was incised and 8 ounces of pus evacuated, no irrigation. Drainage tube of 3½ inches. Temporary relief, but rise of temperature on next day (104° F.). Patient lived seven days after the operation.

The author says that this case resembles Bronner's observation, in several points, viz., in the occurrence together of pleurisy, pneumonia and pyopericarditis, also in the character of the pneumonia, sometimes called "wandering pneumonia;" and in the rise of temperature after the opening of the pericardium.

Boy, aged six and three-quarter years. Admitted with history of a fortnight's illness with cough, fever and pain in the left side. Pus was obtained on exploratory puncture in left pleural cavity. Next day, thoracotomy and removal of 10 ounces of pus. Drainage. Increasing precordial dulness. Exploration of pericardium yielded pus. Incision in fourth interspace; escape of several ounces of creamy pus. Tube drain. Pericardium and empyema took about five weeks to heal. Patient was discharged in good condition two months after admission.

Bronner (operator, Teale): British Medical Journal, February 14, 1891, p. 350.

Girl, aged eleven years. Influenza, pneumonia, and empyema. Thoracotomy of right pleura pericardiotomy. Incision in fourth space 1 inch from sternum; escape of 2 pints of thick pus. Irrigation: Short tube drain. Pericardial cavity was syringed out on eleventh day after operation. Death twenty-six days after the incision into the pericardium; on the sixtieth day of illness. No bacteriological examination of pus. Bronner says that the pneumonia resembled Ribbert's streptococcus pneumonia characterized by great irregularity of the percussory and auscultatory symptoms, by a tendency to spread, and by irregular infiltration of the lung tissue on postmortem examination.

Sievers, R.: Ztschr. f. klin. Med., 1893, xxiii, 26.

Female, aged twenty-two years. Right-sided pneumonia and right empyema pericardiocuretesis. Seven days later pericardiotomy; incision in third space near sternum. Escape of large amount of purulent fluid. Drainage. No irrigation. Left empyema after operation. Death (pyemia) on thirteenth day after pericardiotomy. Bacteriological findings: Bacilli in pus, small short ends, neither pneumococci nor streptococci. Autopsy findings showed pus in pericardial and both pleural cavities, as well as acute nephritic changes.

O'Carroll, J.: Dublin Jour. Med. Sc., 1896, cii, 11.

Male, aged twenty years. Right lobar pneumonia; pleural and pericardial effusion. Aspiration. Incision in fourth intercostal space, between nipple and sternum, on thirty-fourth day. No irrigation. Tube drain, free outflow of pus. Death from heart failure in thirty days after pericardiotomy, and sixty-fourth day of illness. Bacteriological findings: Fraenkel's diplococcus in pus discharged from wound.

Same case as that of O'Carroll in Tr. Royal Acad. Med., Ireland, 1896, xiv, 106.

Bohn, H.: Deutsche med. Wchnschr., 1896, xxii, No. 48, 769.

Male, aged thirty-three years. Influenza pleuropneumonia followed by purulent pericarditis. Tapped three times. Incision in third intercostal space; pus under high pressure escaped on incision of pericardium. Local anesthesia (Schleich). Irrigation, boric acid, gauze drain. Immediate relief and improvement. Recovery in four and a half weeks. Discharged from hospital three months after the pericardiotomy. No bacteriological examination of pus.

Shattuck, F. C. (operator, Porter, C. B.): Boston Med. and Surg. Jour., 1897, cxxvi, 438.

Male, aged twenty-six years. Pneumonia. Pericardial effusion. Left empyema. Pericardiocentesis; incision in fifth left space $1\frac{1}{2}$ inches to left of sternum. Large amount of pus evacuated. Irrigation with salt solution. Drainage with two tubes. Resection of fifth rib, six days later, for better drainage. Empyema; pneumothorax after operation. Recovery. Bacteriological findings: Pneumococcus in pus from pericardium and empyema.

Bjorkman (quoted by Roberts): Am. Jour. Med. Sc., 1897, cxiv, 662.

Girl, aged twelve years. Influenza and pleuropneumonia. Paracentesis of pericardium. Resection of fifth and sixth ribs; pleura opened and sutured after evacuation of some bloody serum. Irrigation with boric acid solution; drainage, two large tubes. Recovery in six weeks. No bacteriological examination of pus.

Bjorkman: Hygeia, 1896, lviii, 189.

(*b*) Broncho:

Imerwol (cf. Rhodes): Annals of Surgery, 1915, lxii, 660.

Boy, aged ten years. Twelve days before admission he fell forcibly upon the left anterior part of his chest. Three days later felt sick and complained of pain in the left side.

Examination. Fever, cough, dyspnea. Temperature, 39°; pulse, 130; respirations, 36; rather diaphragmatic, and left side of thorax remaining immobile in respiration. Dulness on left from clavicle embracing, below, the precardial area, and extending one finger's breadth beyond right sternal line. On the left the dulness continues to axillary line. Signs of fluid in left pleura. Bronchopneumonia and congestion.

Diagnosis. Pleuropericarditis. Aspiration in seventh space, axillary line. No result. Condition gradually worse, with abdominal and precordial pain, loss of sleep from pain and cough. Streptococci in expectoration. Nine days after entrance into hospital an aspiration through fifth left intercostal space in mammary line; pus withdrawn. Operation. Incision 4 cm. long in fifth intercostal space, commencing 1 cm. from left sternal margin. Down to pericardium. Aspirated 250 grams of pus. Cultures showed white colonies, Gram-positive. Rapid fall in temperature.

Patient had a stormy time with the bronchopneumonia, but left the

hospital with normal heart outlines and good action. No retraction of intercostal spaces.

Gengenbach, F. P. (cf. Eliot): Colorado Medicine, 1906, iii, 198. (A case of purulent pericarditis.)

Boy, aged eight years. Admitted as a case of appendicitis. Tentative diagnosis was bronchopneumonia, affecting principally the left lung, with possible pericardial effusion. Three days later pericardial paracentesis; 6½ ounces of thick purulent fluid withdrawn, giving almost immediate relief. Two days later pericardiotomy; after resection of part of fifth rib about 1½ pints of pus evacuated. Drainage tube inserted; discharge free. After first gaining some strength, the patient slowly lost ground, under symptoms of pyemia. Death. Examinations of the purulent discharge showed a double coccus (thought not to be pneumococcus by laboratory interne). Examination of the sputum for tubercle bacilli and pneumococci was made with negative results. According to the postmortem report, the left lung was totally collapsed and compressed to a very small size into the apex of the left chest. In the base of the right lung there was a cavity about the size of a walnut, containing bloody purulent fluid. No communication between the pericardium and lungs or pleura. The collapsed left lung was explained by the fact that the pleura was probably accidentally opened during the operation.

Robinson, H. B. (Case II): British Medical Journal, November 26, 1898, ii, 1605.

Boy, aged four years. Severe bronchopneumonia. Pericardiotomy. Resection of fifth cartilage; pleura not opened. Seropurulent fluid and typical pus from deepest part of sac, about 10 ounces. No irrigation; gauze drain. Death in three days. There was no evidence of and no history to suggest that the whole condition was pyemia. The pus from the pericardium gave on cultivation an almost pure growth of Friedländer's pneumococcus.

2. Empyema.

Ransohoff (cf. Rhodes): Annals of Surgery, 1915, lxii, 660.

Male, aged twenty-eight years. About January 7, 1913, when working, he developed pain in the right side, shortness of breath, cough, and tenacious sputum and came to hospital for treatment. Temperature 102.4°; right lower lobe dull. Crepitant rales and bronchial breathing.

January 14, complained of pain in right side, also pain in precordial region. Pericardial friction rub heard.

January 31, needle introduced in sixth interspace just beyond apex of heart and a quart of pus drawn off.

Operation. Ransohoff. Local anesthesia (cocaine). Sixth rib, 2 inches or rib resected, starting from ½ inch from sternum. Pericardium punctured and pus drawn off. Pericardium opened, liberating about 3 pints of a fairly thick yellowish pus. Pericardium stitched to thoracic wall and gutta-percha drain inserted.

March 5, patient died.

Autopsy. Right lung showed congestion and an infarct in lower portion of middle lobe; pleura normal. Left pleural cavity contained about a quart of greenish pus, and the lung was found compressed into upper part of pleural cavity. It showed infarction and congestion.

Pericardial sac was entirely obliterated except posteriorly below and anteriorly where drainage had been established.

Pancreas, spleen and alimentary canal normal.

Left kidney showed a total infarction due to thrombosis of renal artery. Right kidney was congested.

Imerwol (V) (cf. Rhodes): Annals of Surgery, 1915, lxii, 660.

Boy, aged nine years. Two weeks before admission had chills and fever, pain in left side of thorax, fever high.

Diagnosis. Exudative pericarditis and pleurisy.

May 5, aspiration in axillary region, fifth interspace, gave pus from left pleura.

May 6, aspiration in anterior axillary line, fifth left interspace 300 grams, seropurulent fluid. Aspiration of pericardium, fifth left interspace 3½ cm. from left sternal border gave pus. Improvement.

May 19, thoracotomy in fifth left space, axillary line; 350 grams of pus, drainage tube.

May 20, discovered that the pericardium opens into the left pleura by an orifice. Heart sounds audible and apex beat visible. For the next four days this orifice increased in size. Case gradually improved and discharge lessened. Drains removed July 15, and gauze substituted. Wound cicatrized.

July 20, no retraction of intercostal spaces. Normal. Pus showed pneumococci.

Edwards, W. A.: Transactions of the Medical Society of the State of California, 1893, p. 166.

Girl, aged six years. Empyema; thoracotomy. Pericardiotomy. Incision ½ inch within and above apex beat. Nine ounces of pus removed. No irrigation; tube drain. First improvement; two weeks later aggravation of condition in spite of good drainage. Incision was now made in the eighth interspace at the postaxillary line, 16 ounces of pus were removed, and a tube was inserted. Resection of a portion of three ribs was done later. The patient died within a week after the last operation. In the light of postmortem knowledge it appears that this case was a primary mediastinopericarditis, which within two months was followed by a purulent pleurisy. It would seem that the child presented a primary inflammation of the entire anterior mediastinum, which included the pericardium; the empyema was concomitant through continuity.

Delorme and Mignon: Revue de Chirurgie, 1895, xv, 1008.

Patient was a soldier with left-sided pleurisy following influenza. Empyema. Incision in sixth intercostal space; demonstration of general

pleurisy, with considerable retraction of the lung. General improvement followed, but dyspnea persisted and became greatly aggravated three days after the operation. Paracentesis. Pericardiotomy. Incision 6 cm. in fourth intercostal space; escape of only a few drops of turbid fluid. Patient succumbed to asphyxia a few minutes later; the operation having been too long delayed.

Autopsy findings showed that anterior wall of heart was adherent, about a pint of pus was found behind and at the sides of the adherent heart.

Peters, G. A.: Edinburgh Medical Journal, 1903, xiii, 209. Purulent pericarditis complicated by empyema, operation and recovery.

Boy, aged seven years. Pericarditis, followed by empyema. Pericardium was reached through left fourth interspace, and a considerable quantity of seropurulent fluid. Drainage tube. Considerable improvement. The fluid removed was albuminous and coagulable, and contained Staphylococcus pyogenes aureus. Empyema subsequently developed, fluid aspirated contained the Staphylococcus pyogenes aureus. Thoracotomy yielded 30 ounces of pus. Good recovery.

Ogle, C. and Allingham, H.: Lancet, March 10, 1900, i, 693.

Male, aged thirty-six years. Old purulent encysted pleurisy, no acute course. Resection of 2 inches of fifth cartilage; pleura not opened, incision of pericardium; escape of 15 to 16 ounces of pus. Irrigation with hot water, edges of pericardium were sewn to skin.

Death from weakness in fourteen hours. According to the postmortem findings, the origin of the pericardium appeared to be a collection of pus lying close to the right of the sac between it and the lung and the chest wall, which was the result of a previous pleurisy.

Allen (quoted by Roberts): Am. Jour. Med. Sc., 1897, cxiv, 662.

Boy, aged eleven years. Old empyema. Resection of the sixth rib below and inside nipple. Evacuation of 2 quarts of pus. Irrigation with sterile water, gauze drain. Death in twenty days.

(Personal communication from Dr. D. P. Allen, Cleveland, Ohio.)

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Rhodes: Ann. Surg., 1915, lxii, 660.

MacPhedran: Osler's Modern Medicine, iv, 40.

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D'Agata: Arch. f. klin. Chir., 1912, xcviii, 460.

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Kocher: Chirurgische Operationslehre, 1907, xxxiv, 777.

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Riedel: Zentralbl. f. Chir., 1897, xxiv, 56.

Küttner. Bier-Braun-Kümmell, Chirurg. Operationslehre, 1912, ii, 88.

UNILATERAL RENAL HYPOPLASIA AND DYSPLASIA DUE TO DEFECTIVE ARTERIOGENESIS; RELATION TO SO-CALLED HYPOGENETIC NEPHRITIS

By W. M. L. COPLIN, M.D.
PHILADELPHIA

The facts embraced in this communication are presented in support of a contention that there is a type of renal anomaly of developmental origin which predisposes to, or renders inevitable, some form of nephritis, and that this congenital abnormality is probably primarily a defective arteriogenesis necessarily early in the evolution of the organ; furthermore, it is thought that some evidence, based on morphology, is here presented for the first time. The material upon which the report is based represents an accumulation of four years. In order to establish the thesis enunciated it is necessary to prove (1) that abnormal kidneys reasonably assignable to such a group occur; (2) that they result from defective arteriogenesis; (3) that they are accompanied by, or lead to, cardiorenal phenomena in at least some degree reasonably attributable to the kidney condition.

Kidneys of the type considered have long been known and variously named, and the congenital origin of many fully accepted. Chopart[1] knew that one kidney might be large, the other small. The earlier observers did not differentiate congenital or primary hypoplasia from sclerotic, inflammatory and other forms of secondary contraction or atrophy. Indeed, the term atrophy, frequently used, is not acceptable; it implies wasting. Some of these kidneys have at no time been larger than when found; such are not wasted organs. As applied to these organs the terms rudimentary, fetal

[1] Maladies des Voies Urinaries, Paris, 1830; cited by Gastaldi.

and infantile are also of uncertain interpretation. Teyssèdre[1] used the term renal agenesis; hypogenesis is better. Agenesis should mean absence of the organ; often, however, it is used synonymously with hypogenesis.

LePlay and Fayor[2] call the condition renal disparity and observe that it is an arrest and not an atrophy. Evidently Gastaldi[3] has the same thought and terms it inequality of renal volume, and congenital unilateral atrophy; he restricts these names to kidneys in which both vessels and ureters are present. Braasch[4] evidently recognized this type of lesion, which he included under unilateral atrophic kidney, although it might be congenital or acquired. Cadore[5] and Gerard[6] include relative atrophy, obviously meaning abnormal smallness of one kidney and apply the term absolute atrophy to a more marked lesion. Polack[7] describes the condition of agenesis. Many so-called discoid kidneys[8] belong with this group. Some infantile kidneys of the type described by Geraghty and Plaggemeyer[9] should also be included. The organs and clinical phenomena to which Babes[10] applied the term hypogenetic nephritis and the forms studied by Mironescu[11] and by Jianu and Meller[12] have to do with this type of lesion. The condition is recognized by most authors of text-books and kidneys like those constituting the basis of this article are known to, and adequately described by, practically all systematic writers; the basis of defective angiogenesis, however, is not presented as the essential factor in their evolution.

These kidneys are hypoplastic or defectively developed organs; often they are more, the internal arrangement of cortex and medulla is quite anomalous (see Figs. 1, 2, 3, 5, 7), a sort of dyplasia or cacoplasia.

[1] Thèse de Paris, 1892.
[2] Bull. et Mém. de la Soc. Anat. de Paris, 1909, T. 84, 339.
[3] Thèse de Paris, 1910.
[4] Ann. Surg., 1912, lvi, 726.
[5] Thèse de Lille, 1903.
[6] Jour. de l'Anat. et de la Physiol., 1903, 39th year, 176.
[7] Thèse de Bordeaux, 1908.
[8] Fèrè, Bull. de la Soc. Anat. de Paris, 1881, 417; Legueu, Bull. de la Soc. Anat. de Paris, 1892, 19.
[9] Jour. Amer. Med. Assn., 1913, lxi, 2224.
[10] La Sem. Méd., February 8, 1905; cited by Jianu and Meller.
[11] Beit. zum Studium der Histologie der hypogenetischen Nephritis (rumanisch) Bukarest, 1908; cited by Jianu and Meller.
[12] Centralbl. f. allg. Path. u. path. Anat., September 15, 1912, 774.

Morbid Anatomy. Although both organs may be involved, hypoplasia is rarely, if ever, bilateral and even where both kidneys are implicated, is never truly symmetric; commonly it is restricted to one kidney, the other showing compensatory hypertrophy. Usually the affected organ weighs one-fourth or less, to one-half as much as the other. In five instances I have the weights of both kidneys; the average for the smaller organ is 75.8 gm., and for the larger 140.4; if two cases in which both kidneys are obviously affected be excluded, the average weight of the larger kidney becomes 161.3 gms.; the average for the smaller is but little influenced, being 75.4 gms. The most marked difference in weight is 110 gms., the larger weighing in this case 210 gms., the smaller 100 gms. In four cases the smaller kidney weighed 20, 35, 50 and 60 gms. respectively. Teyssèdre[1] observed an instance in which the involved organ weighed 0.85 gm. Gastaldi,[2] from computations based on original observation and collated data, gives for a man a normal of 152 gms., for left kidney, and 141 gms. for the right.

It is therefore obvious that the affected kidney may weigh less than 1 gm. and anything between that and the normal. The whole kidney need not be involved (several kidneys show this, notably the upper in Fig. 5); one pole may be practically normal or at most but little affected. Anomalies of the genitalia,[3] usually unilateral and on the side of the hypoplastic kidney, frequently accompany renal anomalies of this type; in a case recorded by Lombroso[4] the renal defect was on one side and the genital abnormality on the other. Renal dystopia and misplacements of ovaries or testes have also been noted.

The accompanying reproductions (Figs. 1 to 6 inclusive), from photographs, are, in each instance, one-half normal size and adequately illustrate the gross morbid anatomy. An epitome of known data is included in each legend. I have photographs of all specimens studied; this publication includes a few typical specimens only. With the exception of one pair, all the organs are in the Museum of the Jefferson Medical College. As much histological description as

[1] Loc. cit. [2] Loc. cit.

[3] Secher, Berliner klin. Wchnschr., 1915, 52d year, 487; Jainu and Meller, Centralbl. f. allg. Path. u. path. Anat., September 15, 1912, 774; Besançon, Thèse de Paris, 1889.

[4] Cited by Winter, Arch. f. klin. Chir., 1903, Bd. lxix, 6111.

may be necessary to present the vascular changes and their results will be given when discussing defective arteriogenesis.

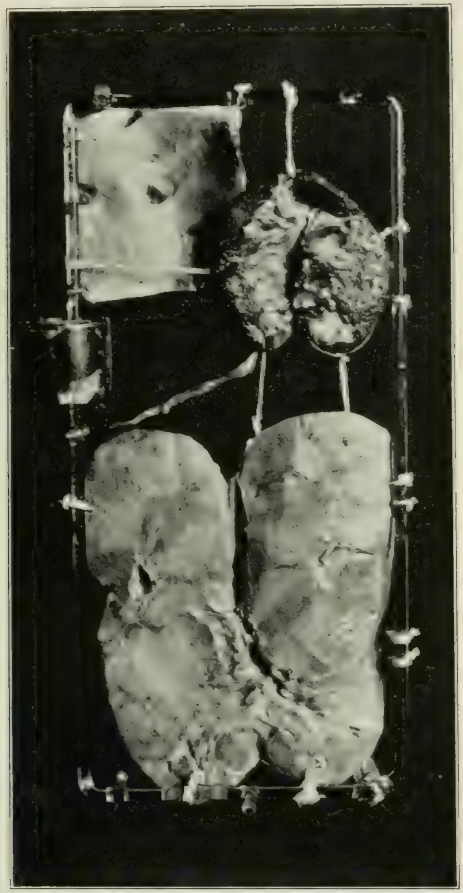

FIG. 1.—Incised surface of kidneys, neither normal; upper organ of infantile type. One-half natural size. M. J.; female; white; aged seventy-three years. Patient and husband insane. Arteriosclerosis; tuberculosis; tuberculous peritonitis. Cardiorenal symptoms (dropsy, stupor, uremia); death. Urine pale: specific gravity, 1010: albumin and casts. Postmortem: Arteriosclerosis. Heart 510 gms. Right kidney (upper) 20 gms. Left kidney (lower) 120 gms. Duplicated renal vessels on both sides. Right kidney of infantile type; vessels nearly obliterated. Distinctions between cortex and medulla imperfect and arrangement abnormal in both organs. Open aorta with abnormal orifices of renal arteries above and to left. See also photograph of other aspect shown in Fig. 2. (Museum No. 1637.)

Of Gastaldi's 66 cases, 10 were females, 32 males and in 18 the sex was not stated. In my series 5 were males, 4 females. Including

the 9 cases on which this report is based, 60 cases have been identified in which the kidney involved is known: 32 right, 28 left. Of 9 patients here reported 3 were negroes.

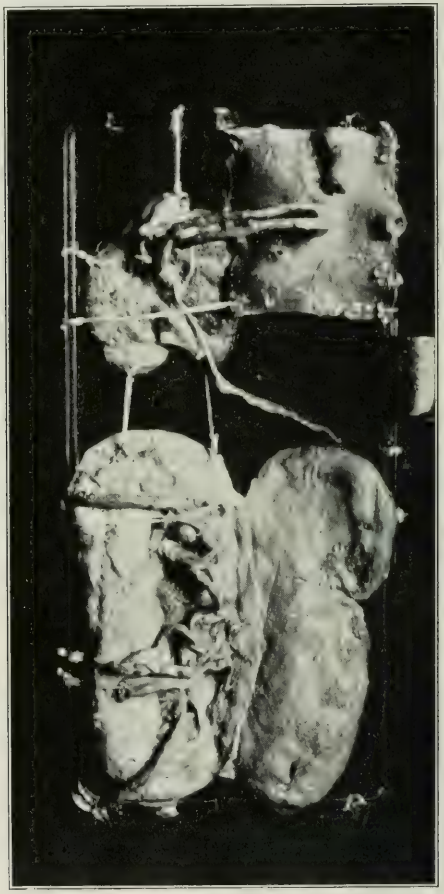

FIG. 2.—One-half natural size. External aspect of opened kidneys shown in Fig. 1. Above and to right external aspect of opened aorta. Smaller kidney supplied by two renal arteries both small and cord-like. Artery to larger kidney came off from aorta as a single trunk dividing at once into two branches both of which are shown on left half of lower organ. Trunks and branches show notable sclerosis superimposed on a congenital anomaly. Clinical data are given in text and in legend to Fig. 1. (Museum No. 1637.)

Concerning the second proposition, namely, that the abnormal kidneys result from defective arteriogenesis, the evidence must be

more carefully weighed. The time is past when doubt as to the vascular origin of certain forms of nephritis can be entertained; arteriosclerotic kidney is universally accepted. When, in this

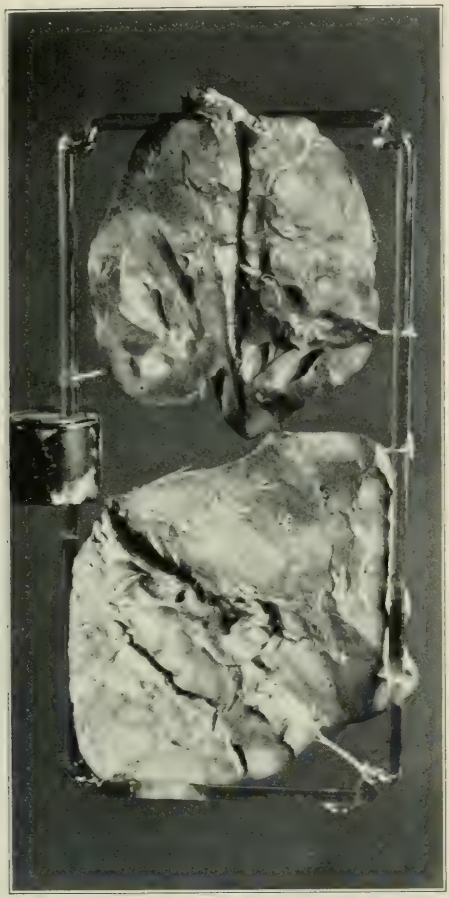

FIG. 3.—Both organs hypoplastic and dysplastic; superimposed alterations of secondarily contracted (arteriosclerotic) kidneys. One-half natural size. Female; colored; aged thirty years. Brought to Hospital in convulsions; unconscious; unequal pupils; urine contained albumin. Coroner's case. Death attributed to septic embolism from infected finger. Postmortem: Pneumonia; pleurisy. Heart weighed 350 gms. No evidence of embolism and no thrombosis found. Moderate arteriosclerosis. Right kidney (upper) 50 gms. Left kidney (lower) 130 gms. Distinction between cortex and medulla possible at points only. (Museum No. 615.)

condition, one kidney is much more changed than the other, or one renal artery more sclerotic than its mate, or, as is not unknown,

when a branch of one renal artery, distributed to one pole of one kidney, is more sclerotic than other branches to other parts of the same kidney, is it not reasonable to assume that some congenital or

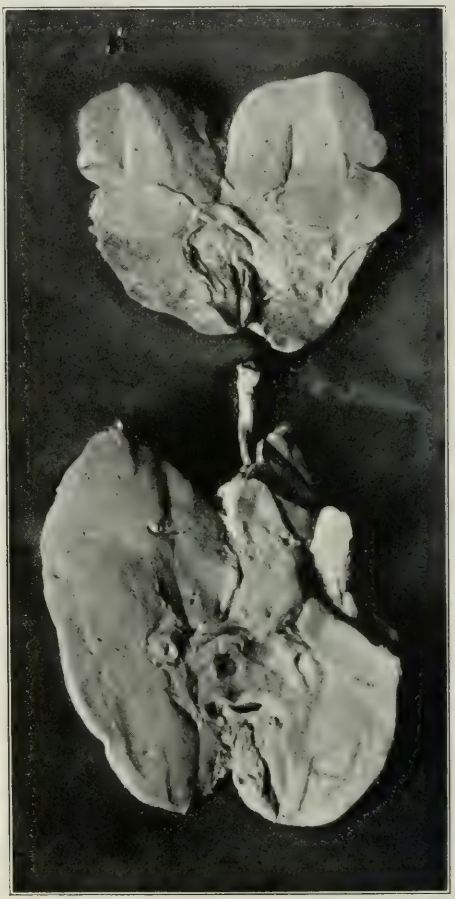

Fig. 4.—Presented through courtesy of Prof. Stengel, Prof. A. J. Smith and Dr. Weidman. One-half natural size. E. H.; female; white; aged twenty-one years. "Always had kidney trouble." In 1912 when six months pregnant, toxemia, albuminuria, miscarriage. January, 1914, therapeutic abortion for toxemia, albuminuria, etc. Blood-pressure known at that time to exceed 212. Recovery with high blood-pressure. Readmitted in August and again in December, 1914. Quantity of urine varied from 750 c.c. to 2825 c.c. Specific gravity, 1007–1010; blood in urine once. Phthalein 33 per cent. in two hours. Wassermann negative. Clinical Diagnosis: Arteriosclerosis; chronic interstitial nephritis. Postmortem: Death due to thrombosis of intestinal vessels. Heart 470 gms. Left kidney (upper) 35 gms. Right kidney (lower) 80 gms. See also text. Sclerotic changes superimposed on congenital anomaly. (Museum No. 2632.)

essential developmental peculiarity has determined the asymmetric distribution of the lesion? The pressure in both arteries must be balanced, the toxicity of the blood, the irritant, destructive or other

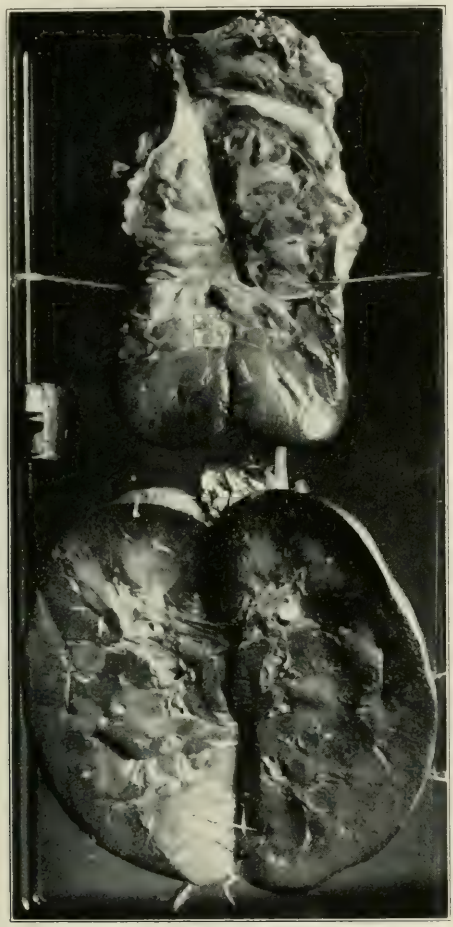

FIG. 5.—One-half natural size. M. S.; male; colored; aged forty-eight years. Cardiorenal case; gastric symptoms predominated early; later dropsy; dyspnea; systolic murmur. Polyuria; trace of albumin; casts; anemia. Diagnosis: Pernicious anemia; syphilis of liver. Postmortem: Hydropericardium; hydrothorax; ascites; gumma of liver. Heart 418 gms. Arteriosclerosis. Left kidney (upper) fused with adrenal, combined weight 132 gms.; 2 arteries, 2 ureters separate to bladder; upper half hypoplastic and dysplastic; small segment of lower pole is practically normal. Right kidney (lower) 198 gms. Slight dysplasia but organ distinctly hypertrophied. (Museum No. 905.)

noxious agents in that fluid must be proffered alike to both arteries and to all branches of the same artery, so that if differences are found, the reasonable assumption is that they resulted from peculiarities

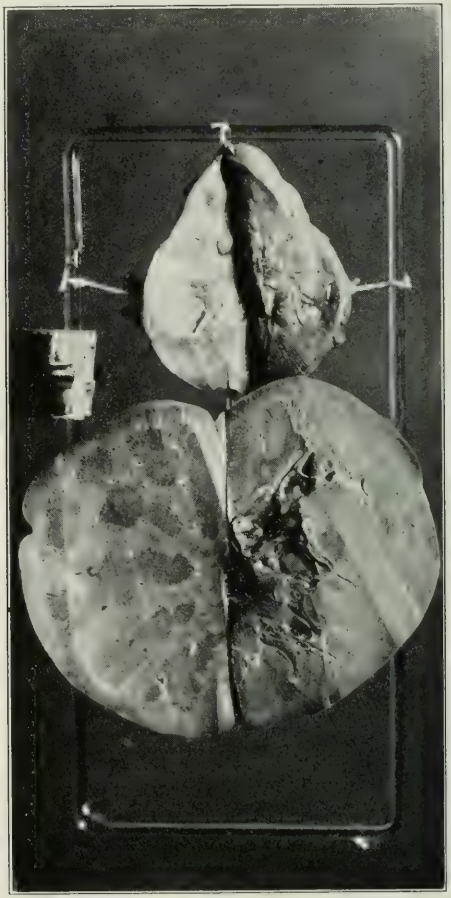

Fig. 6.—One-half natural size. E. D.; female; colored; aged eighty-two years. Had five children; all dead. Disabled by rheumatism. Pain in body and limbs. Edema of legs; ascites; albuminuria; casts; lobar pneumonia; death. Postmortem: Heart 320 gms. Advanced arteriosclerosis. Pneumonia. Left kidney (upper) 110 gms.; hypoplasia and dysplasia; surface but slightly granular. Right kidney (lower) 200 gms. Note absence of normal renal marking; disorderly arrangement of cortex and medulla. Notwithstanding the rather advanced arteriosclerosis neither of these organs is typic of that condition. The larger is clearly hypertrophied, without conspicuous interstitial fibrosis; sections show a degenerative lesion affecting the tubule epithelium with negligible interstitial change; slight glomerular fibrosis. (Museum No. 466.)

of the affected vessel. Resting on known facts, deduction necessarily leads to the conclusion that developmental peculiarity must be a determining factor.

For about a quarter of a century through succeeding editions, Osler[1] has maintained that some patients have better vessels than others; it is reasonable to believe that in the same patient some arteries may be better than others. Lancereaux[2] clearly recognized a relation between congenital narrowing of the vascular tree and nephritis, observing that in some patients the former is at first accompanied by chlorosis, and later by albuminuria with atrophic sclerous nephritis. Gaucher,[3] Rayer[4] and Besançon,[5] contended for a nephritis due to arterial aplasia. Rayer noted a relation between size of the renal artery and the kidney supplied, and that in the same individual the two arteries as well as the organs supplied differed correspondingly in size; of course, this is known to every morbid anatomist. I am not so sure that Gaucher's allusion to nephritis resulting from primitive alteration of anatomical elements refers to defective bloodvessels as the essential basis. Besançon is perfectly clear; to him a subnormal arterial function exerts a deteriorating influence on the kidney, increases its susceptibility to toxic bodies, and may alone determine a primitive interstitial nephritis. He formulated an accompanying clinical picture. Babes[6] notes that walls of renal arteries may be thicker or thinner than normal and that the musculature is usually hypertrophic. The arterial dysplasia so obvious in some of my specimens is quite characteristic. As stated above, my contention is that this is the essential feature; probably all else is secondary. Osteogenesis imperfecta and neurogenesis imperfecta are both fully recognized; why not, as a basis of many anomalies, a defective arteri genesis? In some instances veins and possibly capillaries ar also implicated—defective angiogenesis.

The organ from which was taken the section depicted in Fig. 7 was removed because of recurring attacks of pain; the case, under

[1] Principles and Practice of Medicine, 1892, p. 664; Osler and McCrae, Principles and Practice of Medicine, 1916, 8th ed., p. 842.
[2] Art. Rein. du Dict. Encyclop. des Sci. Med., 1876, 3me Serie, T. 3, 216.
[3] Cited by Besançon.
[4] Ibid.
[5] Thèse de Paris, 1889.
[6] Loc. cit.

the care of Prof. Stewart, will be fully reported elsewhere. The anterior aspect of the kidney showed typic appearance of defective nephrogenesis; artery figured is from within affected side of organ. Observe fragments of elastica in perivascular tissue, irregular external elastic lamina of uneven thickness and notably deficient in waviness. The muscle is abnormally thick and contains more fibrous tissue than muscle. The internal elastic lamina is nowhere

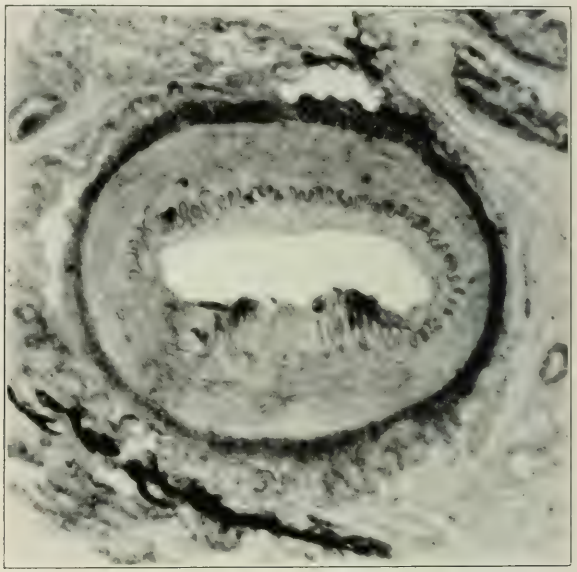

FIG. 7.—Artery supplying involved area of a kidney removed at operation. Fragments of elastica in paravascular tissues; diffuse lime deposit (black) to left and below artery. External elastica almost straight band. Muscle stratum mostly fibrous. Internal elastica atypic, with long sweeping irregular waves notably below. Subintimal proliferation especially marked above. Patient suffered from what was thought to be renal pain or renal angina. Photomicrograph. (Museum No. 2183-B; anterior vessel.)

perfect and below shows long, irregular sweeps never seen in normal vessels. Fig. 8 is a smaller vessel from the same organ; the muscle layer is thick, the elastic lamina (but one layer is present) is irregular and imperfect; a considerable arc (lower left) is without elastica; between elastica and endothelium is a fibrohyalin stratum resembling the substance observed by Gull and Sutton. Of course the arteries shown are not normal; were they ever so? I doubt it.

Fig. 9 (section from organ shown in Fig. 1) shows three arteries, none possessing a lumen proportionate to its size, nor having a normal or vestige of normally distributed elastica; in none is the muscle or intima normal. The organ contained some lime and consequently the section is torn. Below and to the left are groups of hyalin tufts, and a few tubules, two of which are dilated; other

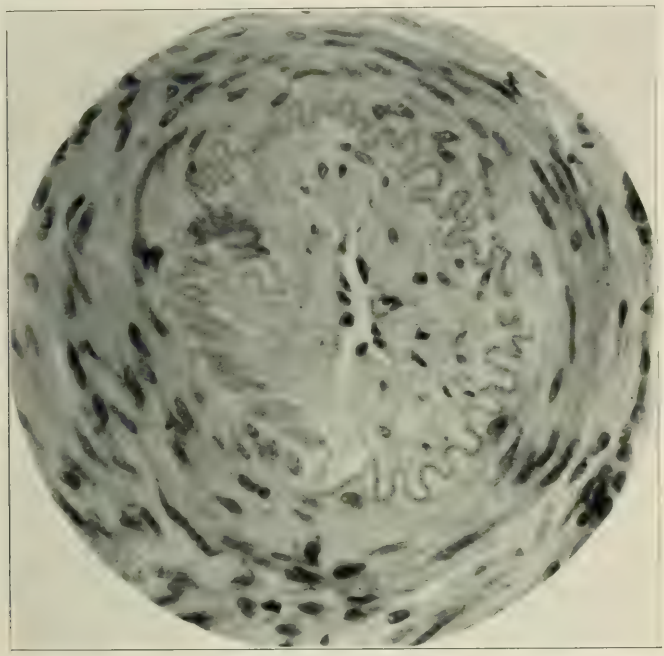

Fig. 8.—Small artery from same case as Fig. 7. Note thick muscle layer; single elastic lamina, imperfect, atypic, and absent from segment below and to the left; break to right; abnormal waviness. Between elastic lamina and slit-like lumen marginated by endothelium note thick fibrohyalin stratum which microchemically gives usual collagen reactions. Arteries from posterior part of this organ did not show these characters or at most but slightly. Photomicrograph. (Museum No. 2183–A; anterior vessel.)

tubules containing hyalin are shown near the center. Of course this patient was old (seventy-three years) and her arteries advancedly sclerotic. The opposite renal artery appeared as sclerotic as those of the small symmetric, miniature or infantile kidney which was probably hypoplastic at birth or became so shortly afterward; the lesions of arteriosclerosis are superposed. Fig. 10 is of an artery from

upper pole of organ shown in Fig. 5. The distorted cortex, thickened capsule, irregular surface, unevenly distributed medulla, and abnormal pelvis of upper half of organ shown in Fig. 5 might have been attributed to the associated arteriosclerosis; however, the fused adrenal extending into the kidney substance could have had no such origin. The artery shown in Fig. 10 possesses a single irregular imperfect elastic lamina inside of which is a thick muscle

Fig. 9.—Section from kidney shown in Figs. 1 and 2. Three abnormal vessels, apparently arteries. See description in text. Note that normal arrangement of lamina is not present nor are the normal layers recognizable. Below larger vessel note calcified content of degenerated tubules; practical absence of normal epithelium. Below to left many hyalin tufts. Photomicrographs. (Museum No. 1637–8–1.)

layer; fragmentation of intima seen in many of these vessels is probably due to contained lime salts. I do not believe that this was ever a normal vessel. In Fig. 11 are two vessels in the midst of a mass of fibrohyalin tissue; the stainable elastica is without its characteristic waves, notwithstanding the fact that obviously both vessels are contracted. To the left is part of another vessel, an artery, with the waveless internal elastica upon which is a thin

cellular layer covered by endothelium. Fragments of the external elastic lamina extend into the surrounding fibrous cellular tissue. In the center of the picture is a cellular area; below and to the left several imperfectly developed Malpighian tufts. Photograph of section from small kidney is shown in Fig. 6.

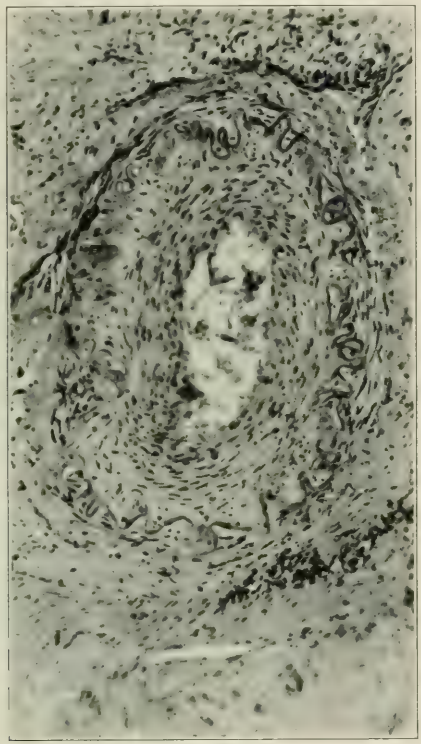

Fig. 10.—Transverse section of artery from upper pole of smaller kidney shown in Fig. 5. Fragments of elastica in paravascular structures; vessel elastica atypic in location and morphology. No muscle external to elastica and abnormally thick fibromuscular stratum between elastica and lumen. Completely detached endothelium. Tissue around vessel is formative in type, contains fibroblasts in varying stages of development. Photomicrograph. (Museum No. 905–3.)

The contention is that these kidneys are never perfectly developed, that the arteries were always defective, and that probably the renal hypoplasia rested upon a nutritive basis. Patients may reach an extreme old age without manifesting symptoms, but when anything calls upon the organs for unusual functional activity they break

down. Such functional inadequacy is well known in congenital heart disease, in the liver when altered by congenital syphilis, and in allied conditions. Meltzer[1] has shown that in many organs, notably the kidneys,[2] there is a generously beneficent excess of our actual needs. We may by various disease processes diminish the abundance perilously close to the danger-point. It is equally certain that the patient may be born without the generous supply usually afforded, or, if adequate at birth, faulty or arrested develop-

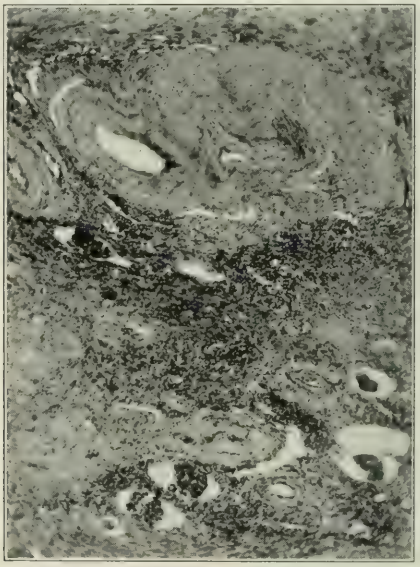

Fig. 11.—Insular fibrosis surrounding small group of imperfectly formed vessels. In center mononuclear infiltration. Below many fibrohyalin glomeruli; others are cellular in centers of dilated tuft spaces. Photomicrograph. (Museum No. 466.)

ment of the kidney may later exert a crippling influence. It is in such position that these patients find themselves. They may pass through life with no renal manifestation, and in such cases the symptomatology which Besançon[3] and also Jianu and Meller[4] and others, have attempted to establish, may be absent. Of 9 cases embraced in this study, in 3 renal disease was clearly indi-

[1] Jour. Am. Med. Assn., 1907, xlviii, 655.

[2] This phase of renal function is fully discussed by Karsner, Bunker and Grabfield, Jour. Exp. Med., 1915, xxii, 544, who also give references to earlier work.

[3] Loc. cit.

[4] Loc. cit.

cated, and in 1 the diagnosis of chronic interstitial nephritis was made with full recognition of associated cardiovascular phenomena; in another the diagnosis was chronic nephritis. One of the patients was brought to the accident ward, admitted unconscious with a provisional diagnosis of uremia, and died during transfer to the ward. In this case no doubt a careful study would have resulted in recognition of the condition. One of the patients operated upon (not one of the 3 just mentioned) had been explored and, because the posterior part of the kidney was normal and the anterior alone affected, the condition was not recognized even at operation. The most carefully studied specimen in the group is the one for which I am indebted to Prof. Stengel. Pregnancy, associated toxemia and eclampsia, with the report that the patient had had kidney trouble all her life, were suggestive; a systolic pressure above 200 mm., and at one observation 230: a trace of albumin; low specific gravity; phthalein elimination 40 per cent. in two hours; non-protein nitrogen 33 to 36 mgs. per 100 c.c. It is probable that ureteral catheterization might have cleared up the case. Besançon[1] lays particular stress upon history of chlorosis or of a chlorotic appearance, headache, vomiting, lassitude, slightly puffy eyelids, slight diffuse edema of lower extremities, frequent micturition, abundant pale urine; obviously none of these alone, nor all together would constitute anything peculiar or characteristic. Nephritis, toxemia, or uremia, coming on in young persons without adequate cause should arouse suspicion. Obviously the *x*-rays and a careful differential study of excretion from the two ureters would be of distinct aid in diagnosis. By the use of these modern methods Dr. Alexander Randall has recognized and operated upon a patient having renal abnormality apparently of this type. With well-known functional tests at present at the disposal of the clinician it would seem that the condition should be recognized, and that, with a knowledge of the possibility of such an anomaly, a closer scrutiny of atypic cardio-renal cases should result. Because of operative risk incident to attack upon the better kidney the condition must be of particular interest to the surgeon.

[1] Loc. cit.

THE MAIN FACTORS AFFECTING THE INTENSITY OF SOUNDS AS THEY PASS FROM THE INTERIOR OF THE LUNGS TO THE PERIPHERY OF THE CHEST

By GEORGE W. NORRIS, M.D.
AND
CHARLES M. MONTGOMERY, M.D.
PHILADELPHIA

The intensity of sound as it passes between two places may vary in one of three ways: It may become intensified, it may remain constant, or it may be diminished. In these general features sound presents certain resemblances to light. Factors operating to increase sounds between the interior of the bronchi and the periphery of the chest are little understood and are probably of very minor importance, as far as the mere intensity of audible sounds is concerned. Factors concerned in maintaining the original intensity of sounds are found particularly within the bronchi, which act much as speaking tubes in preventing, through limitation of diffusion, the weakening of the sounds coming from the upper respiratory tract, while at the same time the bronchi carry the sounds deeply within the lungs, thus preserving a good deal of their original intensity. The bronchi, however, provided they are patulous, and not too far retracted toward the root of the lung, exert their influences on the sounds within them under both normal and pathological conditions, so that to a large extent our interest centers on the sounds *after they have escaped from within the bronchi.* It is not, however, with an increase in sounds, or their retention, that we are chiefly concerned, but with those factors tending to effect a diminution in the intensity of sounds in the chest.

The Diminution of Sounds. The diminution of sounds in different clinical conditions as they pass from the interior of the bronchi to the periphery of the chest, depends chiefly on one or both of two factors: *the diffusion of sounds and the reflection of sounds.*

The Diffusion of Sounds. By diffusion is meant a spreading out of the sound, a dilution of the sound energy. If a sound originates at a point, and, owing to the non-existence of any obstructions, spreads out equally in all directions, the intensity of the sound will be the same on all points of the surface of a sphere whose center is at the point of origin of the sound. At the surface of a second sphere, double the area of the first, and concentric to the same point of sound origin, the vibration energy, per unit of area, and hence the intensity, is halved. This is a deduction from the so-called inverse square law of acoustics, which tells us that, in a medium in which the absorption of energy is small enough to be neglected, and which is extended enough (infinite) so that the complications introduced by boundaries may be disregarded, the intensity of a sound varies inversely as the square of its distance from the source. The importance of the factor of diffusion of sound in diminishing the intensity of sounds as they approach the surface of the chest has, for the most part, been understood in only a very general way, and the great relative importance of this factor in certain clinical conditions has been largely overlooked. Thus, the main factor in determining the diminution of vocal resonance in pleural effusion as contrasted with the normal lung, is diffusion.

The Reflection of Sounds. The reflection of sounds is a form of sound obstruction, and is as different from the diffusion of sound as the reflection of light is from the diffusion of light. Of course we are now speaking of reflection as it interferes with the transmission of sounds on their way to the hearer who is situated distal to the point of reflection, for reflection may intensify sounds by actually focussing them to a smaller area. In the chest we look for factors reducing sounds (exclusive of diffusion) either within the different individual media encountered, or at the junction of different media, that is, where different media occur in combination.

The Different Individual Media Concerned. All the individual media with which we are concerned may be divided into

three groups: (1) the solids, or, better, the gels, which include the tissues, normal and pathological (such as pneumonic consolidation or fibrosis); (2) the fluids, and (3) the gases. It is very easy to show that *each of these individual media by itself offers but little obstruction to the passage of sound through it, and that whatever proportion of sound is lost in its passage through these individual media is due to diffusion.* In the de-intesification of sounds on their way to the periphery of the chest, no differences in the conductive properties of any of these media, solids (or gels), fluids and gases, have been determined by the stethoscope, and therefore are not of present concern to us.

Different Media in Combination. Apart from diffusion, the chief factor in diminishing sounds passing through the chest is the reflection of sounds occurring at the junction of certain of the above-mentioned media. *Comparatively little sound is lost in its passage between fluid and tissue, because their densities are not greatly different and they are both highly elastic. But between air and tissue or air and fluid, provided the body of tissue or fluid is not too attenuated, a very marked "break" occurs, because of the vast differences in density of the adjoining media.* As far, then, as different media in the chest affect sound intensity by their combination, they may be roughly reduced to two: a medium of air and a medium free from air.

To summarize what has been said about the diminution of sound in the chest, we are dealing chiefly with two factors, diffusion and reflection, the former occurring fairly constantly, the latter, for the most part, requiring the presence of air and taking place mainly at the junction of air with either solid (tissue, gel), or fluid. Or, to put it in another way, there is very little diminution of sound in the absence of air, except that due to diffusion, provided the bronchi are patulous and not reduced in size.

In speaking of the combination of tissue and air as offering an obstruction to the passage of sounds, the degree of obstruction will depend on the thickness of the tissue adjacent to the air. Thus, much more sound is lost when the vibrations are passing from air to chest wall, than from air in one of the vesicles in the lung to the delicate enveloping membranous wall. The fact that sounds pass through the normal lung with as little loss as they do, is largely

because each delicate membrane individually offers relatively very little obstruction. *More obstruction occurs when these membranes are tense than when relaxed, the greater tenseness of the membrane in the former case effecting a greater degree of reflection of the vibrations.* The result is the well known clinical fact, that the normal lung in the normally distended state impedes the transmission of sound more than when in a state of collapse. *A great difference in transmissability can be shown to exist when the sounds traverse equal distances in distended and relaxed lungs.*

While the solid tissues of the lung (normal and diseased), and of the chest wall in the living body contain a large proportion of fluid in the form of lymph and blood, this mixture of two different media, fluid and tissue, does not materially reflect or obstruct the passage of sounds, for the reason given, that the densities of tissue (normal and pathological) and fluid are relatively near alike.

The purely solid portions of the tissues we are considering are made up chiefly of soft cellular substance, which, to a large extent at least, is physically allied to gelatin, and belongs to the group of gels, substances which it is well to bear in mind are very different physically from such solid materials as wood and metal. These gels, though potentially capable of yielding a large proportion of fluid, do not actually contain it, just as gelatin, though capable of yielding much water, does not do so as long as it is in the state of gelatin.

Absorption, Resonance and Interference of Sounds. Besides the main factors of diffusion and reflection of sounds there are other factors affecting the intensity of sounds within the chest, but their activities, what little we know about them, appear to be much less influential. On the quality of sounds, however, at least in the case of resonance, their effect may be very marked. By *absorption* is meant the annihilation of sound energy as such, and its conversion into other forms of energy, such as heat, which may not be appreciated by the ear. It is a factor concerned in the diminution of sound intensity quite distinct from diffusion, though at times confused with it. Absorption by different media apparently plays a very small part in the reduction of sound intensity in the chest. *Resonance* acts particularly by affecting sounds of a certain

pitch, and as the chest sounds familiar to us are compounded of many different kinds of individual sounds, resonance usually exerts its influence only on a limited number of these individual sounds. Certain elements in the original sound may be diminished through *interference*, that is, the superimposition of sound waves upon each other.

The size of the bronchi as a factor in determining the intensity of the vocal resonance. When a bronchus, or a group of bronchi, such as we find in the bronchial tree of one lung, becomes reduced in size, the total amount of sound energy coming from the upper respiratory tract and being admitted to these bronchi, is less than when the bronchi possessed their original larger capacity. How much of an effect this decrease in the bronchial capacity may exert upon the vocal resonance requires further investigation. This factor would have a particularly favorable opportunity to operate when the whole lung is much reduced in size, as may occur in pleural effusion or pneumothorax. Braune and Stahel (W. Braune u. H. Stahl, "Ueber des Verhältniss der Lungen, als zu ventilirender Lufträume, zu den Bronchien, als luftzuleitende Röhren," *Arch. f. Anat. u. Physiol.*, 1886, Anat. Abtheilung, S. 5) have shown that the diameter of a bronchus usually depends in part upon the amount of air in the lung, and it seems quite possible that in chronic affections of the lung and pleura the bronchial capacity might become sufficiently reduced to appreciably affect the vocal resonance. The explanation for the greater vocal resonance often encountered normally over the right lung, may rest partly on the fact that the right lung is larger than the left, which necessitates a larger total intrabronchial capacity on the right side, which permits the entrance of a larger amount of sound energy into this side. (The ratio of the diameters of the right and left main bronchi in the normal individual, according to Braune and Stahel, is about 4 : 3, approximately the same ratio that they obtained for the respective weights of the lungs on the corresponding sides.)

The Origin of the Sounds Involved. It is to be recalled that the spoken voice sounds, bronchial breathing, and whispering pectoriloquy arise in the upper respiratory tract, so that the source of these sounds is identical, however variable may be the conditions

in the lungs, and different intensities in different parts of the external chest surface must be due to factors operating distal to the source of these sounds. On the other hand, variations in intensity of the vesicular breath sounds, at least of the inspiratory ones, sounds which arise within the lungs, may be due in whole or in part to differences in intensity at the site of production of these sounds. Thus, in pleural effusion, even if slight, the vesicular murmur may be weakened because there is not proper expansion of the vesicular structure to produce sounds of normal intensity.

The Relative Importance of Different Portions of the Respiratory Passages below the Larynx as Direct Sources of the Vocal Resonance. While the trachea and bronchi resemble speaking tubes to the extent that they transmit within their interior sounds coming from the upper part of the respiratory tract toward peripheral portions of the lungs, the walls of the tracheobronchial tree are, all along the route, taking up a certain amount of the sound present within these air passages. Some of the vibrations entering these walls are never perceived by the auscultator, and, in the case of the normal lung, the vocal resonance over most of the chest is due entirely or largely to vibrations escaping from the smaller bronchi. Under these conditions the trachea and larger bronchi serve only as carriers of sound from the upper respiratory tract to the smaller bronchi. The normal right apex, according to Fetterolf ("The Anatomic Explanation of the Greater Amount of Vocal Fremitus and Vocal Resonance Normally Found at the Apex of the Right Lung," *Archives of Internal Medicine*, February, 1909) receives some audible vibrations that have come directly from the trachea without having had to pass through the bronchi. In pneumonia it has been shown by Mason (*American Journal of Diseases of Children*, March, 1916) that the voice and breath sounds become much altered when a peripherally situated consolidation, previously separated from the large bronchi by an area of normal lung tissue, by extension centrally, finally comes in direct contact with these large bronchi. The large bronchi furnish some of the sound when the lung assumes the fetal type following the disappearance of air from within the alveoli. The trachea itself may be a direct source of sound when the upper part of the

lung is solid, or when the upper portion of the pleural cavity is filled with air or fluid, the pulmonary apex being free from adhesions and retracted toward the root of the lung.

While fully recognizing the limitations of the explanations offered for various auscultatory findings obtained over the lungs, we believe that the application of the simple principles just presented to certain clinical conditions can frequently be determined to a considerable extent. Six of these conditions will receive brief attention: solidified lung, normal lung in a state of normal distention, collapsed but otherwise normal lung, pleural effusion with diminished vocal resonance, pleural effusion with increased vocal resonance, and pneumothorax.

Solid Lung. This is the simplest clinical condition we have to study. In tracing the sounds from within the bronchi through the solid lung to the periphery of the chest we find the factor of diffusion of sound everywhere operative. The activities of this factor are very much limited within the bronchi because the bronchial walls to a great extent reflect the vibrations back into the interior of the bronchi, this reflective action in the smaller bronchi being even more powerful when the lung is solid than when it is normal. Once the vibrations have entered the bronchial walls, however, their further course is pursued entirely through tissue with its associated fluids, the solid lung and chest wall forming practically a single good conducting medium which offers very little obstruction to the passage of the vibrations, so that *nearly all the sound intensity that is lost en route from bronchus to chest periphery is due to diffusion*. In no other common clinical condition do we find so little tendency to the reduction of sounds from reflection as when dealing with a solid lung. And even the degree of diffusion is not greater than that ordinarily encountered. The voice sounds are, therefore, relatively loud, or, as we usually express it, are increased in intensity over a solid lung. In addition the weaker sounds produced in the upper respiratory tract, bronchial breathing and whispering pectoriloquy, become audible at the chest surface, while the normal breath sounds are not heard because they are not produced.

THE NORMAL LUNG NORMALLY DISTENDED. The conditions present in a chest containing normal lung in its normal state of tension offer a marked contrast to those occurring when the lung becomes solidified. Such a lung, unlike the solid lung, does not exhibit a single good conducting medium free from air between bronchial wall and chest wall. Instead, we find air associated in a very peculiar way with the delicate membranous tissues of the pulmonary parenchyma, these membranes at the same time being under a considerable degree of tension. Sound energy is lost: (1) as the vibrations pass from the bronchial walls to the air in the nearest adjoining vesicles; (2) as the vibrations pass between the air in the vesicles and the tense membranous walls enclosing them, and (3) as the vibrations pass from the air in the vesicles immediately underlying the chest wall to the tissues between these vesicles and the chest wall, which practically means to the chest wall. *Each such loss of energy is the result of reflection* acting on the vibrations as they pass toward the exterior of the chest. It is not surprising, therefore, with all these places unfavorable to the transmission of sound that the normal vocal resonance is so much less intense than when the lung is solid. In fact, it is more difficult to explain why the voice sounds are not actually weaker than they are. Two conditions may be mentioned which are relatively favorable to sound transmission when the lung is normal: (1) Sound can more easily escape from within the smaller bronchi to the thin walls of the smaller bronchial tubes of the normal lung than when these tubes become encased in solid tissue. (2) There is some sound conduction even in the thin membranous tissue of the normal lung. The absence of bronchial breathing and whispering pectoriloquy over normal lung is due to the same conditions that make the vocal resonance less than that over solid lung.

RELAXED BUT OTHERWISE NORMAL LUNG. Clinically this condition occurs above a pleural effusion and is apparently responsible for the increased vocal resonance frequently found above an effusion. A good deal of the confusion and error that has resulted in the attempt to explain different degrees of intensity in the sounds heard over the chest has been due to a failure to recognize *the different effects on sound transmission occasioned by the normally distended*

lung and the collapsed lung, or, as it is frequently termed, the compressed lung. Bullar (1884) was the first one to describe the marked differences in conductivity of these two kinds of lungs, though he offered no explanation for this variation. *The relaxed lung allows vibrations to pass through it with less obstruction or reflection than the distended lung*, for the reason given in speaking of the normally tense lung, that is, *because the relaxed membranes of the collapsed lung are not under tension*, and therefore reflect the vibrations backward to a much less extent than when the same membranes are tense. This principle is well known, and can be readily illustrated by passing sounds into a tube and listening at the far end, when it will be noticed that if a thin piece of rubber membrane (or body tissue) is placed across the lumen of the tube at some point, much less sound gets through to the far end of the tube when this membrane is held taut than when it is completely relaxed. The relaxed lung lets more sound through it than the distended lung even when the area traversed in the two cases is identical. In all respects, *except the degree of tension of the finer tissues*, the relaxed and tense lungs are very much alike as far as sound transmissibility is concerned, when equal distances in the two kinds of lungs are compared.

Pleural Effusion with Diminished or Absent Vocal Resonance. The explanations for this phenomenon when not entirely erroneous have been either obscure or incomplete. The abnormal conditions encountered in a simple case are the presence of fluid within the pleural cavity, and a more or less relaxed lung. The clinical fact above referred to, that the vocal resonance above a pleural effusion is frequently increased, indicates that the sounds escape from the relaxed lung to adjacent tissue with more intensity than in the normal case. The evidence indicates that the sounds pass between a relaxed lung and fluid with about an equal intensity to that found in the passage of sounds between relaxed lung and tissue. Therefore, in those cases presenting an increase in vocal resonance above an effusion we conclude that the vibrations entering the fluid are louder than those entering the chest wall of an individual with the lung in a normal state. *Any loss of sound, then, (except as noted below), encountered over a pleural effusion, must take*

place after the vibrations have entered the fluid. We have already seen that tissue alone, and fluid alone, and even the combination of the two, offer very little impediment to the passage of sounds. *The loss of sound encountered over an effusion may be traced largely to diffusion*, the result of the greater distance occurring between the lung and the chest wall overlying the fluid as compared to the close approximation of the lung to the chest wall under normal conditions when no fluid separates them. The sounds become weak over an effusion for the same reason that they do over the liver, because of diffusion and not because of reflection. When the lung is much reduced in size the diminished vocal resonance may be partly due to the decrease in size and capacity of the bronchi, which allows less sound to enter the lung than normally. When effusion is present, the vesicular murmur may be diminished or absent partly because the vesicles are not expanding properly to produce sounds of normal intensity.

Pleural Effusion with Increased Vocal Resonance. The explanations offered to account for an increase in the vocal resonance sometimes met with over a pleural effusion are few and for the most part unsatisfactory. *In some cases this increased vocal resonance is apparently due to the fact that the fluid adjoins a lung which is solid.* The lung may be solid simply from absence of air in the vesicles, as when it assumes the fetal type after prolonged collapse, or it may be solid as a result of inflammatory or other products in the vesicles. It is important that no air should remain in the pulmonary parenchyma. *When a solid lung is separated from the chest wall by fluid, there is very little reflection or other form of obstruction to the passage of vibrations on their way to the periphery of the chest, after they have entered the bronchial walls. Neither the tissues (lung and chest wall), nor the fluid, either individually or in combination, offer any serious impediment to the passage of sounds.* If, then, diffusion is limited, the conditions are very much as in the case of the solid lung unassociated with fluid. And whatever the degree of diffusion, due to separation of the lung from chest wall and other factors, the conditions are very much the same as though tissue replaced fluid in the pleural cavity. The explanation is entirely satisfactory where the solid lung is separated only a short distance from the chest wall by the fluid, but it is well known

that very large effusions on either side of the chest separating the lung a great distance from the chest wall, and thereby increasing the diffusion between lung and chest wall, may furnish striking examples of cases with increased vocal resonance. In such cases it seems likely that some vibrations are received at the periphery of the chest *coming straight across through the fluid from the trachea*. The physical conditions are certainly favorable for this, that is, the fluid may be present in the upper part of the pleural cavity, so that in the course of the vibrations from the trachea to the chest wall no air intervenes, but only tissue and fluid. Very loud sounds may be obtained over the chest of a fetal calf after fluid has been introduced between the chest wall and the solid fetal lung, these sounds becoming much weaker, however, after inflation of the lung. (The sound in this case is introduced into the trachea.)

Pneumothorax. In the case of pneumothorax the distinctive location of sound loss is at *the junction of the air in the pneumothorax cavity with the chest wall*, where reflection of the vibrations acts very powerfully as a result of the enormous differences in density of air and tissue. If the collapsed lung is air-bearing, the opportunities are more favorable for the transmission of sounds to the periphery of the chest than if the lung is solid, because more sound can enter and leave a collapsed air-bearing lung under these conditions than when the lung is solid, while at the same time the air-bearing lung itself is a very good transmitter of sound. If no adhesions exist at the apex, sound may be obtained coming directly from the trachea to the chest periphery by way of the pneumothorax cavity. *Diffusion exerts little effect between the lung and the chest wall*, the sound intensity being fairly equal throughout the pneumothorax chamber, because the air is enclosed within solid walls. The diminished vocal resonance is probably partly due to the small size of the collapsed lung and the consequent diminished calibre of its bronchi, resulting in the admission of a reduced amount of sound into the affected lung. When a patulous fistula exists between the pneumothorax cavity and a bronchus, the conditions are favorable for abnormally loud vocal resonance.

The various subjects briefly presented in this paper are further discussed in the *Tenth Report of the Henry Phipps Institute for*

the Study, Treatment, and Prevention of Tuberculosis, in an article by Montgomery and Eckhardt, entitled "Pulmonary Acoustic Phenomena."

DISCUSSION

Dr. George W. Norris, Philadelphia, said that the credit for the work presented belonged to Dr. Montgomery and Mr. Eckhardt. Dr. Norris had merely stimulated the research. One important point brought out by Dr. Montgomery's work was the reason why certain cases of pleural effusion yield bronchial breathing with increased fremitus and vocal resonance. Whether or not these signs will be present, or whether the classical text-book signs of pleural effusion exist, depends on the character of the underlying lung. If this is solid, the signs will be those of consolidation, since there is no marked break of conductivity in the transmitting media.

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